The Effect of Curcumin on Lipid Level in Patients with Acute Coronary Syndrome

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ABSTRACT

Aim: *to evaluate the effects of curcumin on total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride in acute coronary syndrome patients.*

Methods: *this study were conducted at Dr. Cipto Mangunkusumo General Hospital (RSUPN-CM), Persahabatan Hospital, MMC Hospital and Medistra Hospital, Jakarta. The study started from 1 May 2005 to 5 May 2006. Study Design was an interventional study which was a randomized double blind controlled trial to evaluate the effects of curcumin administration at escalating doses (low dose 3 times 15 mg/day, moderate dose 3 times 30 mg/day, and high dose 3 times 60 mg/day) on total cholesterol level, LDL cholesterol level, HDL cholesterol level, and triglyceride level in ACS patients.*

Results: *a 75 ACS patients undergoing randomization participated in randomized controlled trial (RCT). Of the 75 ACS patients participating in that RCT, 67 received care at RSCM, 6 at Persahabatan Hospital, and 2 at MMC Hospital. As many as 63 patients were able to participate in the RCT up to its conclusion.*

There was no significant difference in age, sex, risk factor of dyslipidemia, DM, smoking, hypertension, CHD history in family, height, body weight and body mass index, waist circumference, systolic blood pressure, diastolic blood pressure in the four groups of patients. This showed that the randomization performed was reasonably good. There was no significant difference in laboratory parameters, such as total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride, fasting blood glucose, blood glucose 2 hours PP, glyco Hb, triglyceride, Hb, Ht, leukocyte, thrombocyte, ureum, creatinine, SGOT, SGPT, in the four groups. There was no significant difference in types of ACS and locations of ACS in the four groups as well.

There was no significant difference in statin medicatios (simvastatin), aspirin ACE inhibitor, and DM medications in the four groups. No patient used tiazolidindion. No significant difference was found in the percentage of compliance in the four groups of patients.

The effects of curcumin on total cholesterol level and LDL cholesterol level, there was a trend that the lower the dose of curcumin, the higher the effect of reduction. For HDL cholesterol level, there was also a trend that the lower the dose of curcumin, the higher the effect of increase in HDL cholesterol level. However, for triglyceride the pattern was not the same, and the group of moderate-dose curcumin shoed the minimal effect of increase, followed by the low-dose curcumin and finally the high-dose curcumin that showed the highest effect of increase.

Conclusion: *the administration of low-dose curcumin showed a trend of reduction in total cholesterol level and LDL cholesterol level in ACS patients.*

Key words: *curcumin, lipid level, triglyceride, blood glucose.*

INTRODUCTION

Curcumin is an extract of turmeric (*Curcuma longa/ Curcuma domestica)* and temulawak (*Curcuma xanthorrhizae*), which are native Indonesian plants. Such plants are members of the ginger family (*Zingiberaceae)* and have been widely used as raw materials for traditional medicines.[1-2]

There has been lack of studies about the effect of curcumin on metabolic factors and usually the studies are conducted for experimental animals. Tortosa et al.,[3] reported that administration of turmeric extract inhibited the oxidation of low density lipoprotein (LDL) and it has hypocholesterolemic effect in rabbits with experimental atherosclerosis. Babu et al.,[4] also reported the hypolipidemic effect of curcumin in induced-diabetic rats. A study by Arafa,[5] in experimental animals fed with

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high-cholesterol diet indicated that curcumin has hypocholesterolemic effect i.e. it decreased serum total cholesterol by 21 % and LDL cholesterol by 42.5%, but it increased serum HDL cholesterol by 50%.

Therefore, it is very interesting to study whether curcumin has hypolipidemic effect (i.e. reduce absorption of and increase enzyme activity of cholesterol-7á-hydroxylase) in human, particularly in patients with acute coronary syndrome (ACS), which has characteristic of dyslipidemia as one of its risk factors.

This study is the first study that evaluates the effect of curcumin on lipid profile of patients with ACS, as one of serial studies about the effect of curcumin on metabolic factor and inflammatory response in patients with ACS.

METHODS

This study was an interventional study, a randomized double blind controlled trial, which was designed to evaluate the effect of curcumin with escalating dose (low dose, moderate dose, and high dose) on total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides level in patients with ACS. The study was conducted at ICCU of National Central General Hospital Cipto Mangunkusumo Hospital, Faculty of Medicine, University of Indonesia, ICCU of Persahabatan Hospital, ICCU of MMC Hospital and ICCU of Medistra Hospital. The time of study was from May 2005 to May 2006.

Study Subjects

Subjects of the study were patients with ACS hospitalized at ICCU of Cipto Mangunkusumo Hospital, who were examined and followed since their admission up to next 2 months. A small number of subjects were patients hospitalized at ICCU of Persahabatan, MMC and Medistra Hospital.

The patients' informed consents were obtained after they had explanation from the investigator/ assistant investigators. Approval of the study was obtained from Institutional Ethical Committee Faculty of Medicine, University of Indonesia.

Sample Size Calculation

In this part, we would like to answer a question, i.e.: does administration of curcumin will change the value of metabolic factor and inflammatory response in ACS. For the design of this study, we used the formulation of t-test for 2 paired group to calculate the sample size, i.e. $n = (SB^2 (za + zb)^2) /d^2$, with expected higher power, i.e. 90 % (or b = 0.1, zb = 1.28).

The inclusion criteria were: (1) patients with ACS who were hospitalized at ICCU of Cipto Mangunkusumo Hospital, at ICCU of Persahabatan, MMC and Medistra Hospital who had fulfilled the ACS criteria with onset < 72 hours, (2) willing and able to provide informed consent for study participation.

The exclusion criteria were: (1) having acute or chronic infection; (2) has other concomitant disease correlated to inflammatory response such as autoimmune disease, connective tissue disorder, and malignancy, trauma or operation in the last 1 month period; (3) having treatment of corticosteroid, NSAID or immunosuppressant; (4) having statin treatment in the CHD group; (5) for the ACS group, the statin has been administered only after the blood sample for inflammatory response has been taken (before the intervention) (for observational study); (5) having treatment of tiazolidindione; (6) having chronic liver or kidney disease

Parameters/Documented Variables

History taking: age, sex, education level, ethnicity, previous chest pain and myocardium infarction, smoking habits, previous treatment, history of hypertension, DM, dyslipidemia, and heart disease in the family. Physical examination: blood pressure, heart examination, body height, weight, waist circumference.

Clinical laboratory: peripheral blood count: hemoglobin, hematocrit, leukocytes, platelets; CK, CKMB, troponinT, fasting blood glucose and 2 hours PP, glyco Hb, total cholesterol, direct LDL cholesterol, HDL cholesterol, and triglycerides, ureum, creatinine, AST, ALT.

Acute coronary syndrome (ACS)[6,7]: a wide spectrum of cardiac emergency consists of: ST elevation myocardial infarction (STEMI), non ST elevation myocardial infarction (*NSTEMI*), unstable angina pectoris (UAP).

Unstable angina pectoris[8] (with any of following criteria): 1). Angina occurring at rest and prolonged, usually greater than 20 minutes; 2). New onset angina of at least Canadian Cardiovascular Society Grading Scale (or CCS classification system) classification severity III; 3. Recent acceleration in angina accentuated by an increase in severity of at least 1 CCS class to at least CCS class III.

Canadian Classification of Angina[9]: I. Angina only occurs with strenuous exercise; II. Moderate exertion, such as climbing more than 1 flight of stairs causes angina; III. Mild exertion, such as climbing less than 1 flight of stair causing angina. IV. Angina at any level of physical exertion, even at rest.

Acute myocardial infarction[10]: a typical raised and gradual decrease of troponin value or increase an rapid decrease of myocardium necrosis biochemical marker should be accompanied by at least one of the following: a. Ischemic symptoms; b. the development of pathological Q waves on the ECG; c. ECG changes indicating ischemia (ST segment elevation or depression); d. coronary artery intervention (for example, coronary angioplasty).

Coronary Heart Disease (CHD): were patients with coronary heart disease who did not have acute coronary syndrome based on history taking and ECG but has demonstrated to have CHD based on previous coronary angiography or had experienced acute myocardium infarction at least in 6 months prior to the examination.

Type 2 DM: diagnostic criteria of type 2 DM (The Indonesian Consensus on Type 2 DM Management, PERKENI 2002[11]): 1. Random glucose level (venous plasma)> 200 mg/dL; or 2. Fasting blood glucose level (venous plasma) > 126 mg/dL or; 3. Post-prandial plasma glucose level > 200 mg/dl after 2 hours of 75 gram glucose load during oral glucose tolerance test.

Age: It was calculated during the study based on the Identity Card. If the age was > 6 months, it was upgraded; and if < 6 months, it was downgraded. Body weight: was measured in kilogram (kg) units using SECA digital 770 weighing scale. Body height: was measured in centimeter (cm) units, by using Microtois CMS tool. Body mass index (BMI): in kg/m^2, was calculated by using the following formula: body weight (kg)/ body height $(m)^2$. Waist circumference was measured by SECA 200 *Measuring Tape.* Total cholesterol level by enzymatic method of CHOD PAP by Roche. Direct LDL cholesterol was measured by homogeneous method of Daichi. HDL cholesterol was measured by homogeneous method of Daichi. Triglycerides level was measured by using enzymatic method of GPO-PAP.

Curcumin

The curcumin extract was taken from the root (*rhizome)* of turmeric (*Curcuma domestica*), which was produced under supervision in appropriate to the standard processing procedure of pharmaceutical materials in Cianjur. Analysis on aerobic bacteria, fungi, *E. Coli*, *S. Aureus* and *Pseudomonas aeruginosa* indicated negative results. Analysis of curcumin concentration was performed by using HPLC method, at the Laboratory of Great Central Research and Development of Post-Harvest Agriculture.

Determination of the curcumin dose applied in this study was based on the phase I study by Cheng et al.[12], i.e. there was no side effect occurs in patients with advanced stage of cancer who used the curcuma extract up to 8 gram, equal to 180 mg curcumin for 4 months. Such dose was the highest curcumin dose that had ever been used in clinical trial for human. In this study, high dose curcumin of 180 mg/day was administered in a dose of 60 mg three times daily as the previous studies showed that the plasma curcumin level will decrease in 8-12 hours. The moderate-dose of curcumin was half of the high dose, i.e. 90 mg/day, given 30 mg three times daily; while the low-dose curcumin was a quarter of the high-dose, i.e. 45 mg/day given as 15 mg three times daily.

Curcumin was given for 2 months considering the study by Ramirez-Bosca et al.[13], which demonstrated that the curcuma extract has exerted significant effect of reduced lipid peroxides in 2 month period.

Data Collection

For routine blood test and blood chemistry test, samples of peripheral venous blood were taken after a fasting period (10-12 hours), and then 2-hour post-prandial blood glucose were taken and sent according to the standard procedure to the Clinical Laboratory. For examination of IL-6 level, the blood samples were taken from the vein in accordance to standard procedure and sent to the Clinical Laboratory.

Consecutive sampling of patients with ACS was performed in patients who were hospitalized at ICCU of Cipto Mangunkusumo Hospital, Persahabatan, MMC and Medistra Hospital RSUPN-CM, ICCU RS Persahabatan, RS MMC, RS Medistra since May 2005 until May 2006.

Randomization

The effect of curcumin was evaluated against total cholesterol, direct LDL cholesterol, HDL cholesterol, and triglycerides. The curcumin groups were divided into 3 sub-groups: 1. Low-dose: 3 x 15 mg. 2. Moderate-dose: 3 x 30 mg. 3. High-dose: 3 x 60 mg.

Randomization was performed by using computer with block-random method, i.e.: 15 patients in group 1 received 15 mg curcumin (low dose), 15 patients in group 2 received placebo, 15 patients in group 3 received 30 mg curcumin (moderate dose), 15 patients in group 4 received placebo and 15 patients in the group 5 received 60 mg curcumin (high dose).

Processing Technique and Data Analysis

All of continuous data collected was coded, tabulated by using STATA and calculated statistically. Parametric test was performed on variables with normal distribution; while variables with abnormal distribution were transformed so that the parametric test

can be performed. All of the calculation used the significance level of $p < 0.05$, which was calculated by using the STATA program. In order to demonstrate the evidence for the effect of curcumin on total cholesterol level, LDL cholesterol, HDL cholesterol and triglycerides in patients with ACS, paired t-test was performed.

RESULTS

Subject Characteristics

There were no significant differences on age, sex, risk factors of dyslipidemia, DM, smoking, hypertension, history of CHD in the family, BH, BW, BMI, waist circumference, BP systolic, and BP diastolic among the four groups. This indicates that the randomization has been performed quite well.

There were no significant differences on laboratory parameters such as total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides, fasting blood glucose, 2-hours PP blood glucose, glyco Hb, triglycerides, Hb, Ht, leukocytes, platelets, ureum, creatinine, AST, and ALT among the four groups.

There was no significant difference of the ACS type and location among the four groups.

Table 1. Demographical and physical characteristics of the low-dose (LD) curcumin group, moderate-dose (MD) curcumin group, and high-dose (HD) curcumin group and the placebo group

Variables	Placebo n = 26 (%)		Curcumin LD n = 15 (%)		Curcumin MD n = 14 (%)		Curcumin HD n = 15 (%)	
	mean	SD	mean	SD	mean	SD	mean	SD
Age, year	54.31	8.55	58.6	13.73	54.29	9.47	54.47	8.70
Sex, M/F	23/3		10/5		11/3		12/3	
Risk factors								
Dyslipidemia	9 (34.62)		4 (26.67)		6 (42.86)		2 (13.33)	
DM	7(26.92)		6 (40)		5 (35.71)		6 (40)	
Smoking	15 (57.69)		6 (40)		5 (35.71)		6 (40)	
Hypertension	17(65.38)		5 (33.3)		4 (28.57)		6 (40)	
CHD in the family	9 (36.42)		4 (26.67)		6 (42.86)		2 (13.33)	
Physical examination								
BH (cm)	161.73	7.45	159.19	11.33	159.74	6.90	159.57	8.18
BW (kg)	67.78	12.62	63.87	12.68	64.43	10.88	63.99	12.46
BMI(kg/cm2)	25.81	3.89	25.06	3.19	25.12	2.82	25.05	3.68
Waist circumference (cm)	89.97	12.40	86.66	9.14	87.96	9.60	86.40	9.86
BP systolic, mmHg	124.15	20.43	118.4	27.27	117.93	19.82	122.67	15.90
BP diastolic,mmHg	75.23	14.11	71.00	16.92	71.29	14.50	73.67	10.18

Table 2. Laboratory characteristics of the low-dose (LD) curcumin group, moderate-dose (MD) curcumin group, and high-dose (HD) curcumin group and the placebo

Variables	Placebo n=26		Curcumin LD n=15		Curcumin MD n=14		Curcumin HD n=15	
	mean	SD	mean	SD	mean	SD	mean	SD
Laboratory Parameters								
Total cholest, mg/dL	207.23	58.23	202.67	59.64	211.71	55.18	190.87	36.17
LDL cholest, mg/dL	148.73	49.36	139.07	55.07	149.5	40.84	133.87	33.49
HDL cholest, mg/dL	38.04	8.80	42.13	10.44	40.50	9.15	41.13	8.82
Triglycerides, mg/dL	146.15	63.18	151.53	91.37	145.64	47.99	119.40	34.08
Nuchter BG, mg/dL	130.58	69.13	118.27	37.80	123.50	43.34	114.87	23.94
2-hours PP BG, mg/dL	148.85	61.81	155.73	61.45	176.79	108.79	156.27	53.95
Glyco Hb, %	6.75	1.60	7.31	1.98	7.25	1.93	7.17	1.72
Hb, g/dL	14.06	1.75	13.65	1.66	14.41	2.57	12.97	2.24
Ht, %	40.67	5.59	39.70	4.92	41.99	7.60	38.00	6.29
Leuko, cell/mL	13.23	4.95	12.17	4.62	12.46	4.82	12.09	3.53
Platelet, thousand cells/mL	271.77	66.61	258.8	81.42	276.64	71.07	256.87	50.43

There was no significant difference of statin drug (simvastatin), aspirin, ACE inhibitor and the DM drugs among the four groups. None of patient had used tiazolidindione.

There was no significant difference of compliance percentage among the four groups.

The Effect of Curcumin on Total Cholesterol Serum

On Table 5 and Figure 1, we can see the effect of curcumin at low dose, moderate and high dose on total cholesterol level compared to the placebo group.

In the low-dose curcumin group, the log of total cholesterol level after 2-month intervention (5.23) was lower than before the intervention was performed (5.25) (p=0.40). In the moderate-dose curcumin group, the log of total cholesterol level after 2-month intervention (5.25) was lower than before the intervention was performed (5.29) (p=0.34). In the high-dose curcumin group, the log of total cholesterol level after 2-month intervention (5.34) was higher than before the intervention (5.22) (p=0.99). In the placebo group, the log of total cholesterol level after 2-month intervention (5.25) was lower than before the intervention (5.30) (p=0.15).

In Figure 1, it is apparent that the total cholesterol level after 2-month intervention in low-dose, moderate-dose curcumin group and the placebo group are lower than total cholesterol level before the intervention; however, there is no statistically significant different. The total cholesterol level in high-dose curcumin group is

Table 3. Characteristic of heart disorder in the low -dose (LD) curcumin group, moderate-dose (MD) curcumin group, and high -dose (HD) curcumin group and the placebo group

Variables	Placebo n = 26	Curcumin LD n = 15	Curcumin MD n = 14	Curcumin HD n = 15
	mean (SD)	mean (SD)	mean (SD)	mean (SD)
Type of ACS				
STEMI	21(80.77)	10(66.67)	10(71.43)	8(53.33)
non STEMI	3(11.54)	3(20)	3(21.43)	5(33.33)
UAP	2(7.69)	2(13.33)	1(7.14)	2(13.33)
Location of ACS				
Anteroseptal	8(30.77)	3(20)	2(14.29)	4(26.67)
Anterior	2(7.69)	1(6.67)	5(35.71)	0(0)
Anterior extensive	4(15.38)	3(20)	6(42.86)	2(12.33)
Anterolateral	1(3.85)	0(0)	0(0)	2(13.33)
Inferior	2(7.69)	3(20)	0(0)	1(6.67)
Inferior & Right Ventricle	0(0)	1(6.67)	0(0)	0(0)
Inferoposterior	4(15.38)	3(20)	0(0)	1(6.67)
Posterior	1(3.85)	0 (0)	0(0)	1(6.67)
Inferoposterolateral	0(0)	0(0)	0(0)	1(6.67)

Table 4. The treatment characteristic in the low -dose (LD) curcumin group, moderate -dose (MD) curcumin group, and high -dose (HD) curcumin group and the placebo group

Variables	Placebo n = 26 (%)	Curcumin LD n = 15 (%)	Curcumin MD n = 14 (%)	Curcumin HD n = 14 (%)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Antiplatelet				
Aspirin	25(96.15)	15(100)	13(92.86)	13(86.67)
Other drugs				
ACE inhibitor	22(84.62)	12(80)	12(85.71)	15(100)
Beta blocker	15(57.69)	10(66.67)	12(85.71)	15(100)
Statin	13(50)	6(40)	7(50)	7(46.67)
Drugs for DM (outpatient)				
No drugs received	23(88.46)	14(93.33)	12(85.71)	11(73.33)
Insulin	0(0)	0(0)	0(0)	2(2.86)
Sulfonil urea (SU)	1(3.85)	1(6.67)	0(0)	2(13.33)
Biguanid (metformin)	2(7.69)	0(0)	1(7.14)	0(0)
Combination biguanid + SU	0(0)	0(0)	1(7.14)	1(6.67)
Tiazolidindione	0(0)	0(0)	0(0)	0(0)
Drugs for DM at ICCU				
Insulin	5(19.23)	4(26.67)	4(28.57)	6(40)
Compliance	91.90 (8.79)	88.19 (9.84)	94.80 (7.11)	93.19 (7.05)

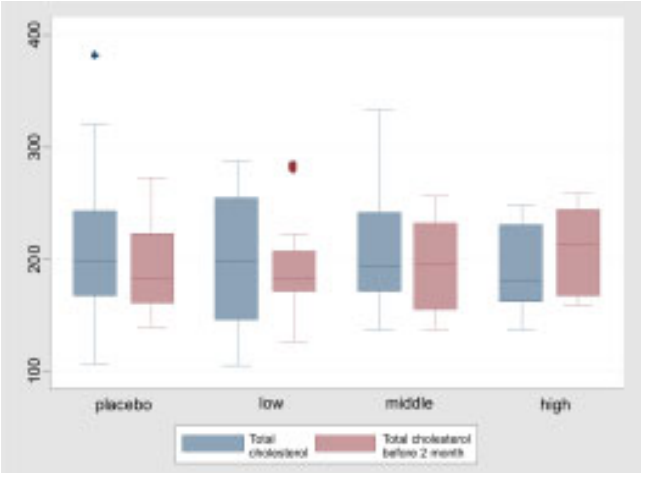

Figure 1. Total cholesterol level in patients with ACS before and after 2 month intervention according to the curcumin dose

Table 5. Log mean of total cholesterol level in patients with ACS before and after 2-month intervention and the percentage mean of its changes according to the curcumin dose

Variables	Log. Mean of Total Cholesterol Level				Mean Percentage of Changes
	Before Intervention		After 2-month Intervention		
	Mean	SD	Mean	SD	
Curcumin LD (n=14)	5.25	0.32	5.23	0.24	-2.10
Curcumin MD (n=11)	5.29	0.26	5.25	0.22	-0.20
Curcumin HD (n=14)	5.23	0.20	5.34	0.18	+0.30*
Placebo group (n=24)	5.30	0.28	5.25	0.21	-2.40

* p < 0.05 placebo vs intervention group

higher compared to before the intervention, but there is no statistically significant difference.

Total cholesterol level after 2-month intervention was lower in the low-dose and moderate-dose curcumin group, as well as the placebo group; however, there was no statistically significant difference. The log of total cholesterol level in high-dose curcumin group was higher compared to before the intervention, but there was no statistically significant difference.

The mean percentage of changes for total cholesterol level in low-dose curcumin group after 2-month intervention compared to before the intervention decreased 0.20% than the placebo group, which showed a decrease of 2.4%, with p=0.70.

The mean percentage of changes for total cholesterol level in moderate-dose curcumin group after 2-month intervention compared to before the intervention increased 0.30% than the placebo group, which decreased 2.40%, p=0.61.

The mean percentage of changes for total cholesterol level in high-dose curcumin group after 2-month intervention compared to before the intervention increased 12.50% than the placebo group, which indicated a decrease of 2.4 %, with p=0.98.

A trend of decreased percentage is observed best in the low-dose curcumin group, followed by moderate-dose curcumin group and finally in the high-dose curcumin group (positive increase)

The Effect of Curcumin on LDL Cholesterol Level

In Table 6 and Figure 2, we can observe the effect of low-dose, moderate-dose and high-dose curcumin on LDL cholesterol level compared to the placebo group.

In the low-dose curcumin group, the log of LDL cholesterol level after 2-month intervention (4.78) is lower compared to before the intervention (4.81) (p=0.41). In the moderate-dose curcumin group, the log of LDL cholesterol level after 2-month intervention (4.84) is lower compared to before the intervention (4.93) (p=0.21). In the high-dose curcumin group, the log of LDL cholesterol level after 2-month intervention (4.98) is higher compared to before the intervention (4.86) (p=0.98). It is likely that the low-dose curcumin shows the best decrease percentage. In the placebo group, the log of LDL cholesterol level after 2-month intervention (4.76) is lower compared to before the intervention (4.95) (p=0.01).

Figure 2 shows that the LDL cholesterol level after 2-month intervention in low-dose and moderate-dose curcumin group decrease compared to before the intervention. On the contrary, in high-dose curcumin group, the LDL cholesterol level is higher compared to before the intervention. In the placebo group, the LDL cholesterol level 2-month after intervention is lower than before the intervention.

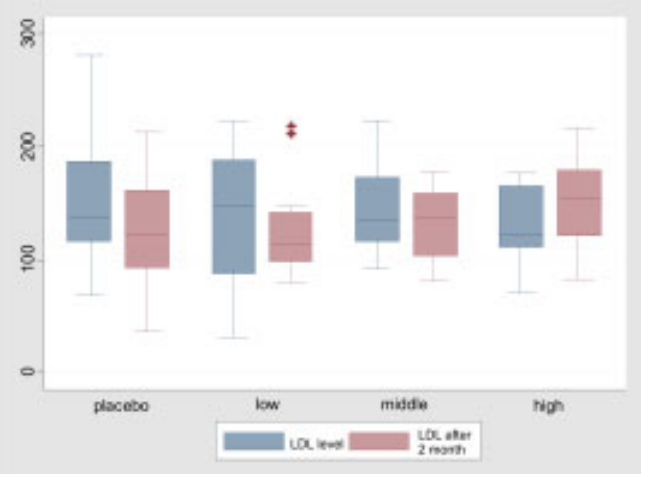

Figure 2. The LDL cholesterol level in patients with ACS before and after 2 month intervention according to curcumin dose

LDL cholesterol level after 2-month intervention in low-dose and moderate-dose curcumin group decrease compared to before the intervention. In the high-dose curcumin group, the log of LDL cholesterol level is higher compared to the intervention. In the placebo group, the log of LDL cholesterol level was lower than before the intervention.

The mean percentage of changes for LDL cholesterol level in low-dose curcumin group after 2-month intervention compared to before the intervention increases 8.6% compared to placebo group, which decreases 11.6%, p=0.92.

Table 6. Log mean of LDL cholesterol level in patients with ACS before and after 2-month intervention and its percentage mean of change according to curcumin dose

Variables	Log Mean of LDL Cholesterol Level				Mean Percentage of Changes
	Before Intervention		After 2-month Intervention		
	Mean	SD	Mean	SD	
Curcumin LD (n=14)	4.81	0.52	4.78	0.32	-8.60
Curcumin MD (n=11)	4.93	0.27	4.84	0.24	-3.40
Curcumin HD (n=14)	4.86	0.28	4.98	0.27	+15.40
Placebo group (n=24)	4.95	0.34	4.76 [a]	0.41	-11.60

a. $p < 0.05$ before vs 2-month after the intervention

The mean percentage of changes for LDL cholesterol level in moderate-dose curcumin group after 2-month intervention compared to before the intervention decreases 3.4 % compared to the placebo group, which decreases 11.6 %, p=0.76.

The mean percentage of changes for LDL cholesterol level in high-dose curcumin group after 2-month intervention compared to before the intervention increases 15.4 % compared to the placebo group, which decreases 11.6 %, p=0.66.

Table 6 shows a pattern of escalation dose, i.e. the higher dose of curcumin, the higher percentage of increased LDL cholesterol compared to before the intervention. Low-dose curcumin shows the highest percentage decrease.

The Effect of Curcumin on HDL Cholesterol Level

Table 7 and Figure 3 demonstrate the effect of low-dose, moderate-dose and high-dose curcumin on HDL cholesterol level compared to placebo group.

In the low-dose curcumin group, the log of HDL cholesterol level after 2-month intervention (3.75) was higher compared to before the intervention (3.71) (p=0.36). In the moderate-dose curcumin group, the log of HDL cholesterol level after 2-month intervention (3.66) was higher than before the intervention (3.60) (p=0.09). In the high-dose curcumin group, the log of HDL cholesterol level after 2-month intervention (3.74) was higher compared to before the intervention (3.69) (p=0.23). In the placebo group, the log of HDL cholesterol level after 2-month intervention (3.68) was higher compared to before the intervention (3.61) (p=0.06).

Figure 3 shows that the HDL cholesterol level after 2-month intervention in low-dose, moderate-dose and high-dose curcumin group was higher compared to before the intervention. Moreover, the HDL cholesterol level in placebo group was higher after 2-month intervention compared to before the intervention.

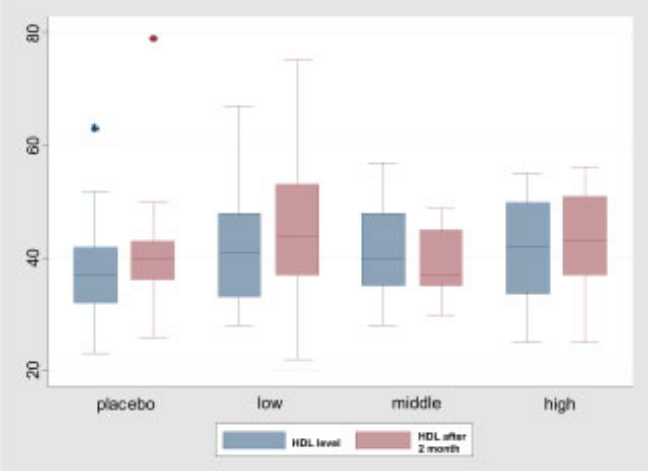

Figure 3. HDL cholesterol level in patients with ACS before and after 2 month intervention according to curcumin dose

HDL cholesterol levels after 2-month intervention in low-dose, moderate-dose and high-dose curcumin group are compared to HDL cholesterol level before the intervention. However, there was no statistically significant difference. Furthermore, the log of HDL level after 2-month intervention in placebo group was also compared to before the intervention. But there was no statistically significant difference.

The mean percentage of changes for HDL cholesterol level in low-dose curcumin group after 2-month intervention compared to before the intervention increases 11.3% compared to placebo group, which increases 10%, p=0.55.

The mean percentage of changes for HDL cholesterol level in moderate-dose curcumin group after 2-month intervention compared to before the intervention increases 7.7% compared to placebo group, which increases 10%, p=0.39.

Table 7. Log mean of HDL cholesterol level in patients with ACS before and after 2-month intervention and its percentage mean of changes according to curcumin dose

Variables	Log Mean of HDL Cholesterol Level				Mean Percentage of Changes
	Before Intervention		After 2-month Intervention		
	Mean	SD	Mean	SD	
Curcumin LD (n=14)	3.71	0.25	3.75	0.32	+11.30
Curcumin MD (n=11)	3.60	0.19	3.66	0.16	+7.70
Curcumin HD (n=14)	3.69	0.23	3.74	0.24	+7.70
Placebo group (n=24)	3.61	0.23	3.68	0.22	+10

The mean percentage of changes for HDL cholesterol level in high-dose curcumin group after 2-month intervention compared to before the intervention increases 7.7 % compared to placebo group, which increases 10 %, p=0.39.

The increased percentage of HDL cholesterol level in low-dose curcumin group demonstrates the highest result compared to moderate-dose and high-dose curcumin group as well as the placebo.

The Effect of Curcumin on Triglyceride Level

Table 8 and Figure 4 shows the effect of low-dose, moderate-dose and high-dose curcumin on triglycerides level compared to the placebo group.

In the low-dose curcumin group, the log of triglycerides level after 2-month intervention (4.91) was higher than before the intervention (4.86) (p=0.64). In the moderate-dose curcumin group, the log of triglycerides level after 2-months intervention (5.04) was higher compared to before the intervention (5.02) (p=0.55). In the high-dose curcumin group, the triglycerides level after 2-month intervention (4.87) was higher than before the intervention (4.73) (p=0.95). In the placebo group, the log of triglycerides level after 2-month intervention (4.98) was higher than before the intervention (4.91) (p=0.06)

Figure 4 shows that the triglycerides level after 2-month intervention was higher compared to before the intervention in low-dose, moderate-dose and high-dose curcumin group. Moreover, the triglycerides level after 2-month intervention in placebo group was higher compared to before the intervention.

The triglycerides level after 2-month intervention in low-dose, moderate-dose and high-dose curcumin group was higher than before the intervention. But there was no statistically significant difference. The log of triglycerides level in placebo group after 2-month intervention was higher than before the intervention, but there was no statistically significant difference.

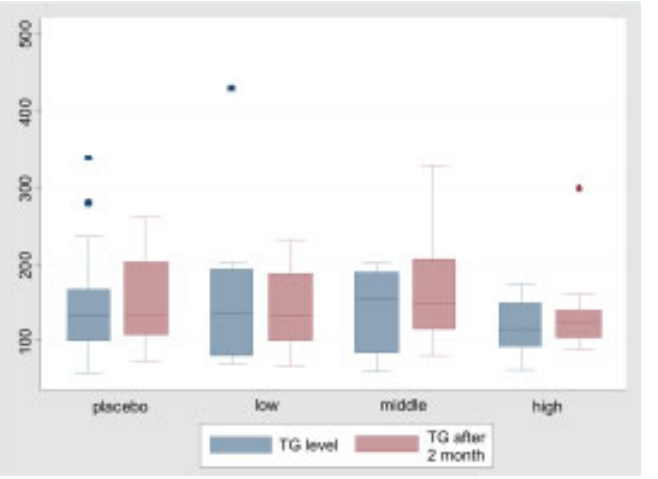

Figure 4. Triglycerides level in patients with ACS before and after 2 month intervention according to the curcumin dose

The mean percentage of changes for triglycerides level in low-dose curcumin group after 2-month intervention compared to before the intervention increases 17.97% compared to placebo group, which increases 14.90 %, p=0.57.

The mean percentage of changes for triglycerides level in moderate-dose curcumin group after 2-month intervention compared to before the intervention increases 10.30 % compared to placebo group, which increases 14.90%, p=0.40.

Table 8. Log mean of triglycerides level in patients with ACS before and after 2-month intervention and its percentage mean of changes according to curcumin dose

Variables	Log Mean of Triglycerides Level				Mean Percentage of Changes
	Before Intervention		After 2-month Intervention		
	Mean	SD	Mean	SD	
Curcumin LD (n=14)	4.86	0.51	4.91	0.42	+18
Curcumin MD (n=11)	5.02	0.31	5.04	0.39	+10,30
Curcumin HD (n=14)	4.73	0.31	4.87	0.30	+20,40
Placebo group (n=24)	4.91	0.41	4.98	0.35	+14,90

The mean percentage of changes for triglycerides level in high-dose curcumin group after 2-month intervention compared to before the intervention increases 20.4% compared to placebo group, which increases 14.90 %, p=0.55.

A trend of increased percentage was observed. The highest was the high-dose curcumin group and lowest was the moderate-dose curcumin group.

DISCUSSION

The Effect of Curcumin on Lipid Level

No study has been reported about the effect of curcumin on lipid level in patients with coronary heart disease. This study is the first study that demonstrates the effect of curcumin on lipid level in patients with acute coronary syndrome.

Ramirez-Bosca et al.[13] in a non-randomized study reported that the extract of curcuma of 200 mg dose for 60 days in healthy lowers the lipid peroxidation by 25-50%.

In this study, the effect of low-dose and moderate-dose curcumin slightly lowers the total cholesterol, but there was no significant difference with the placebo. Although they are not significantly different to the placebo, there was increased effect of high-dose curcumin on total cholesterol level by 0.3%. Ramirez Tortoza et al.,[3] found hypocholesterolemic effect in rabbits fed by a high-cholesterol diet. The mechanism is assumed through increased cholesterol excretion in the gall bladder together with decreased saturation of biliary cholesterol and increased fat excretion in the feces.[3]

In the case of the curcumin effect on LDL cholesterol level, the low-dose has demonstrated the highest decrease (-8.6%), followed by the moderate-dose (-3.4%) and the worst effect has been demonstrated in the high-dose, i.e. an increase by 15.4%. However, it was not significantly different when compared to the placebo. Considering the existed pattern, there was an effect of escalating dose, i.e. the highest the curcumin dose, the worse effect of curcumin occur on LDL cholesterol (moderate-dose curcumin shows lowering effect by 3.4%; while the high-dose curcumin increasing the LDL cholesterol level by 15.4%). The mechanism of such escalating dose pattern has not been known. Ramirez-Tortosa et al.,[3] found that oral administration of turmeric extract inhibits LDL oxidation and has hypocholesterolemic effect in rabbits with experimental atherosclerosis. The group that treated with low-dose of turmeric extracts by 1.66 mg/kgBW decreased the susceptibility of LDL to lipid peroxidation (lowering the serum lipid peroxide level); but there was no effect on the higher dose of 3.2 mg/kgBW. Moreover, the lower dose had lower levels of cholesterol level, phospholipids and triglycerides in LDL than the higher dose. Such study indicated that the antioxidant properties of turmeric extract was dose-dependent. Some studies also reported that anti-oxidant may also have pro-oxidant properties depending on the dose. A study by Hussain and Chandrasekhara[3] showed that there was a dose-dependent response with 0.2, 0.5 and 1% curcumin supplemented lithogenic diet, i.e. 0.5% curcumin was more effective than a diet with 0.2 or 1% curcumin in reducing gall-stone formation.

The effect of curcumin on HDL cholesterol regarding the pattern of escalating dose demonstrated that low curcumin dose has the highest increase up to 11.3%, which was followed by the moderate and high dose with 7.7% increase of each; however, there was no significant difference compared to the placebo group. There was similar pattern to total cholesterol and HDL cholesterol level, i.e. the low dose demonstrated the best result.

In addition, regarding the effect of curcumin on triglycerides, there was an increase of 10.3% in moderate dose, followed by the low dose with an increase of 18% and the worst result was in the high-dose curcumin, i.e. an increase of 20.4% compared to the placebo effect which showed an increase of 14.9%; however, there was no significant difference with placebo in all dose groups.

Ramirez-Bosca et al.[13] reported the effect of curcuma on lipid level (a study of before- and after-design, not a randomized clinical trial) in 30 healthy subjects, (16 male and 14 female) aged 24-70 years. The study demonstrated the effect of hydroalcoholic extract of *curcuma longa* on apo B/apo A ratio. Patients were given 2 tablets of hydroalcoholic extract of *curcuma longa* daily, which were equal to 10 mg per tablet (20 mg/day) for 30 days. There were significant decrease on Apo B/Apo A ratio, decrease Apo B, increase Apo A, reduced LDL cholesterol and increased HDL cholesterol.

Babu et al.,[4] reported hypolipidemic effect of curcumin in streptozotosin-induced diabetic rats and fed with 0.5% curcumin for 8 weeks. The cholesterol level decreased significantly in rats fed with curcumin diet. In order to understand the mechanism of lowering cholesterol in curcumin diet, a measurement was taken on the activity of hepatic cholesterol-7a-hydroxylase and HMG coA reductase. It was apparent that the hepatic cholesterol-7a-hydroxylase level was significantly higher in diabetic rats fed with curcumin, which demonstrated higher cholesterol catabolism rate.

CONCLUSION

This study shows that there is a tendency of low-dose curcumin reduces total cholesterol and LDL cholesterol level. There is also a tendency that the higher the curcumin dose, the lower its lowering effect on LDL cholesterol level, such as the moderate-dose curcumin. In high-dose curcumin, there is a tendency of increased total cholesterol and LDL cholesterol level.

This study demonstrates a tendency of low-dose curcumin to increase the HDL cholesterol level. Moderate and high-dose have a tendency to cause less increase of HDL cholesterol.

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