Investigation of the effect of short-term supplementation with curcuminoids on circulating small dense low-density lipoprotein concentrations in obese dyslipidemic subjects: A randomized double-blind placebo-controlled cross-over trial

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Short Communication

Abstract

BACKGROUND: Small dense low-density lipoprotein (sdLDL) is a sub-fraction of LDL considered to have the most atherogenic properties. The present trial aimed to assess changes in circulating sdLDL concentrations following supplementation with curcuminoids, polyphenolic compounds with diverse potential cardio-protective functions.

METHODS: This study was designed as a randomized double-blind placebo-controlled cross-over trial. A total of 30 obese dyslipidemic subjects were assigned to curcuminoids (1 g/day) or placebo for 4 weeks, followed by a 2-week washout and then treatment with the alternate for another 4 weeks. Serum sdLDL was measured at baseline and weeks 4, 6, and 10 of the trial.

RESULTS: Supplementation with curcuminoids (1 g/day) did not cause any significant alteration in serum sdLDL ($P > 0.05$).

CONCLUSION: Four-week supplementation with curcuminoids was not associated with any significant alteration in circulating sdLDL concentrations.

Keywords: Diferuloylmethane, Curcuma longa L., Turmeric, Cardiovascular Disease, Hypercholesterolemia, Atherosclerosis

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Introduction

Overweight and obesity are major public health concerns in both developed and developing world. These conditions are major determinants of chronic diseases such as diabetes, hypertension, and metabolic syndrome.[1,2] In addition, obesity is often accompanied by dyslipidemia and increased susceptibility to atherosclerosis and coronary heart disease (CHD).[3]

There are two major subclasses of low-density lipoprotein (LDL) based on particle properties: large buoyant LDL that predominates in the pattern A profile (particle diameter ≥ 25 nm) and small dense LDL (sdLDL) that is the predominant form in pattern B (particle diameter < 25 nm).[4] Predominance of pattern B and increased formation of sdLDL particles is a recently discovered feature of atherogenic dyslipidemia.[5]

In addition, sdLDL has greater potential for permeation into the arterial wall and sub-endothelial space, lower interaction with LDL receptor, longer plasma half-life, more susceptibility to modification (e.g., glycation) and less resistance to oxidative stress.[6-9] It has been reported that patients with a predominant sdLDL phenotype have a higher risk of developing CHD compared with those with the large buoyant LDL phenotype. Further, circulating concentrations of sdLDL appear to serve as a useful biomarker for the severity of CHD.[5-7]

Curcuminoids are polyphenolic compounds accounting for most of the biological and medicinal effects of Curcuma longa L. (turmeric). During the past three decades, there has been a substantial

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body of research on the pharmacological properties of these phytochemicals leading to the identification of numerous health benefits.[10-20] Among these benefits are cardio-protective functions that are secondary to the interaction of curcuminoids with several types of receptors, enzymes, hormones, inflammatory mediators, and transcription factors.[21-23] Moreover, there has been in-vitro and in-vivo evidence on the modulation of lipoprotein metabolism and lipid profile by curcuminoids.[20] In spite of some findings on the impact of curcuminoids on conventional lipid profile parameters [comprising total cholesterol, LDL-cholesterol (C), triglycerides, and high-density lipoprotein cholesterol (HDL-C)], no study has yet investigated changes in circulating concentrations of sdLDL, as a novel CHD risk factor and the risk marker, following supplementation with curcuminoids. The present study aimed to evaluate this in a group of obese dyslipidemic subjects.

Materials and Methods

This study is a post-hoc analysis performed on the samples obtained from our previous investigation (IRCT2013082914521N1).[19] The original study was conducted at the Ghaem Hospital of Mashhad, Iran, between 21/08/2010 and 20/08/2012. The study population included men and women aged 18-65 years with a body mass index (BMI) > 30 kg/m^2 who were not originally on lipid-lowering therapy. Other inclusion criteria were the presence of either < 2 risk factors (except diabetes mellitus) for CHD + 160 mg/dl < LDL-C < 190 mg/dl, or ≥ 2 CHD risk factors (except diabetes mellitus) and 130 mg/dl < LDL-C < 160 mg/dl. Individuals with BMI ≤ 30 kg/m^2, history of CHD and history of consuming lipid-lowering medications or supplements within the preceding 6 months were excluded. Thirty subjects were randomized to receive curcuminoids (1000 mg/day + 5 mg piperine for absorption enhancement) or matching placebo (5 mg piperine) as their first intervention. The duration of treatment with either curcuminoids or placebo was for 4 weeks and then each subject was assigned to the alternate intervention following a 2-week washout phase. The primary efficacy parameter change in serum sdLDL levels. Thirty subject completed trial and their blood samples were stored for analyses. Among these completers, the samples of 22 subjects were available for sdLDL assay comprising 12 samples in the placebo-curcuminoids arm and 9 samples in the curcuminoids-placebo arm (Figure 1). There was no pre-specified guideline for interim analysis and study discontinuation owing to the well-documented safety of curcuminoids.

Randomization was carried out by alternative allocation of patients to encoded capsules with the first code being chosen randomly. Both curcuminoids (C3 Complex®) and piperine (Bioperine®) were prepared and encapsulated by the Sami Labs Ltd., Bangalore, India and were completely identical in shape, size, and color. The study protocol was approved by the Ethics Committee at the Mashhad University of Medical Sciences (date: May 12, 2012; code: 88313).

Fasted blood samples (after an overnight fast) were collected from each subject at 4 time points, that is, at the start and end of each intervention period. Samples were then centrifuged at 10,000g for 15 min to obtain serum. Sera were kept at −80 °C until analysis. Blood pressure recordings were conducted after rest using a stethoscope and calibrated mercury sphygmomanometer calibrated by the Iranian Institute of Standards and Industrial Research. The appearance of the first sound (Korotkoff phase 1) was defined as systolic blood pressure (SBP) and the disappearance of the sound (Korotkoff phase 5) during cuff deflation was defined diastolic blood pressure (DBP). Measurement of weight was performed with the subjects dressed in light clothing after an overnight fasting using a standard scale with an accuracy of ± 0.1 kg. Measurement of height was performed to an accuracy of ± 0.1 cm. Waist circumference was measured at the midpoint between the lower rib margin and top of the iliac crest. Hip circumference was measured at the widest point over the buttocks. Total body fat percentage were assessed using a calibrated stand-on Bio Impedance Analyzer (BIA) (Tanita-305 Body Fat Analyzer, Tanita Corp., Tokyo, Japan) with a CV of < 1%). In order to minimize the impact of physiological factors on body fat percentage, BIA was used under constant conditions, that is, fasted state and before exercise. Anthropometric parameters including weight, height, BMI, waist and arm circumference and body fat were measured using standard procedures as described previously.[19,24]

The statistical analysis software SAS (version 9.1, SAS Institute Inc., Cary, NC, USA) was used for statistical analysis. A mixed model analysis of variance for 2 × 2 crossover studies was fitted when assumptions for normality were met. A two-sided P-value of < 0.050 was considered to be statistically significant.

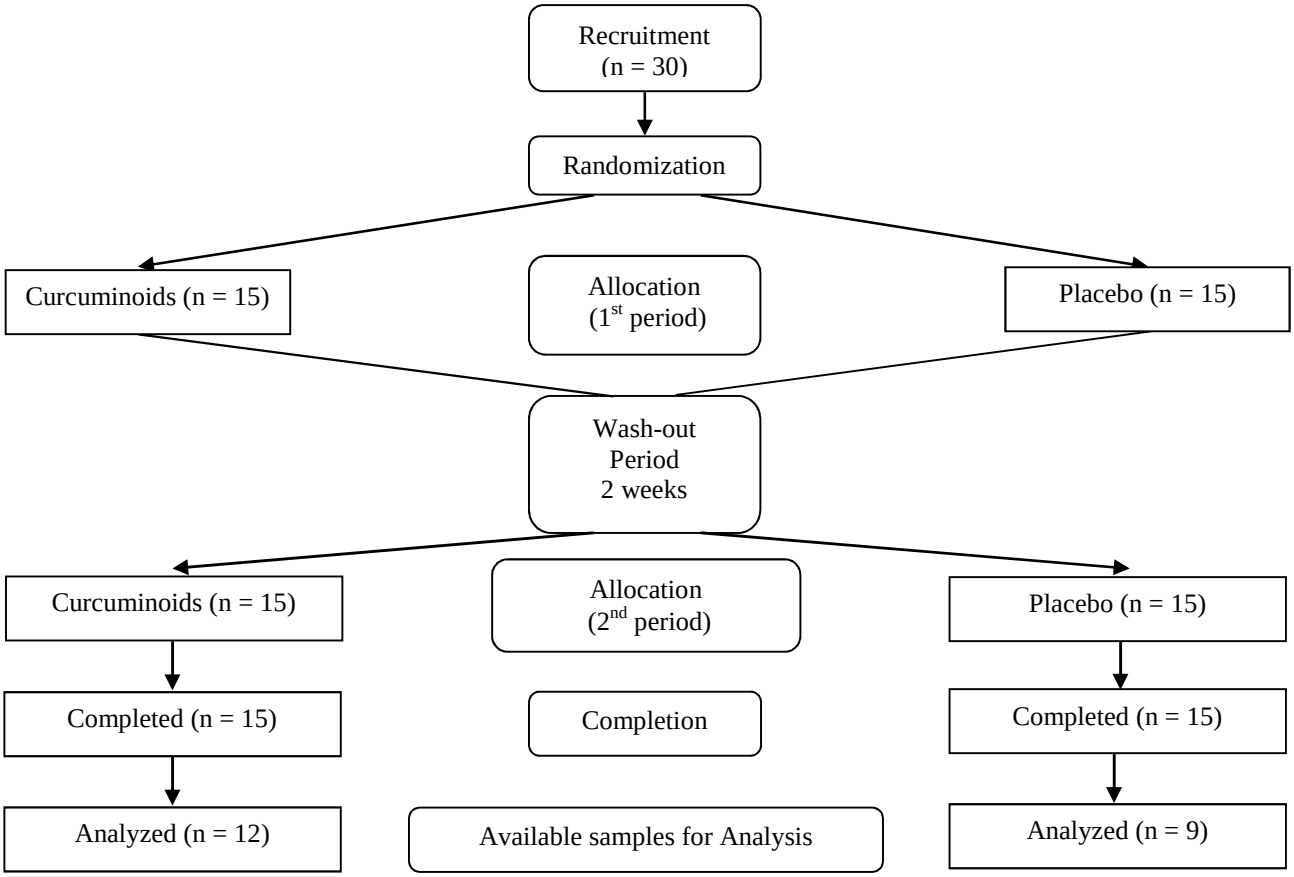

Figure 1. Flow chart of trial

Serum sdLDL was determined using the method described by Hirano et al.[25] Briefly, a precipitation reagent (150 U/ml heparin-sodium salt and 90 mmol/l $MgCl_2$) was added to 0.5 ml of serum sample, mixed and incubated for 10 min at 37 °C. Samples were then placed in an ice bath and left for 15 min, and centrifuged for 15 min at 4 °C. The concentration of sdLDL-apolipoprotein B in the heparin-Mg supernatant was measured by an immunoturbidimetric assay (Biosystems, Spain). The coefficients of variation for inter- and intra-assay were 1.3-1.6% and 1.7-3.7%, respectively.

Results

Demographic characteristics of study population are summarized in table 1. Curcumin-placebo and placebo-curcumin groups were comparable in baseline parameters including age, gender, weight, height, BMI, waist and hip circumference, waist/hip ratio, and SBP and DBP. The only factor with significant baseline difference was fat percentage, which was higher in the curcumin-placebo group (P = 0.019). Baseline sdLDL was also comparable between the study groups (P = 0.472).

Supplementation with curcuminoids (1 g/day) did not cause any significant change in serum sdLDL by the end of the trial (P = 0.820). This effect was found to be robust and not subject to any carry-over, period or sequence effect (P > 0.050). Changes in serum sdLDL in the four assessed intervals are illustrated in figure 2.

Discussion

Findings of the present trial did not indicate any significant effect of 4-week curcuminoids supplementation on circulating levels of sdLDL. Recently, there has been increasing interest in lipoprotein particle size and composition as additional risk factors for atherosclerosis. This is in part due to the observations of normal lipid profile in a considerable fraction of patients with documented CHD. sdLDL particles have been proposed as a sub-fraction of LDL associated with more atherogenic risk, while the larger buoyant LDL particles are much less atherogenic.[26,27] Certain constituents of lipid metabolism, that is, lipoprotein lipase, hepatic lipase, and cholesterol ester transfer protein (CETP) have been shown to contribute to the formation of sdLDL particles.[28,29]

Table 1. Demographic characteristics of study population

Parameter	Curcumin-placebo	Placebo-curcumin	P
Female (%)	89.50	75.00	
Age (year)	38.84 ± 11.12	37.81 ± 12.31	0.797
Height (cm)	158.50 ± 6.36	159.94 ± 9.64	0.601
Weight (kg)	85.57 ± 12.95	83.83 ± 17.43	0.737
BMI (kg/m^2)	33.95 ± 3.81	32.66 ± 4.69	0.373
Waist circumference (cm)	110.34 ± 10.41	106.53 ± 10.43	0.289
Hip circumference (cm)	117.97 ± 9.85	115.07 ± 9.31	0.379
Waist/hip ratio	0.94 ± 0.06	0.93 ± 0.05	0.606
Fat percentage (%)	41.25 ± 5.49	36.48 ± 5.83	0.019
SBP (mmHg)	118.84 ± 13.29	117.62 ± 10.99	0.772
DBP (mmHg)	79.63 ± 10.21	80.44 ± 8.41	0.803

Values are expressed in mean ± SD; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure
SD: Standard deviation

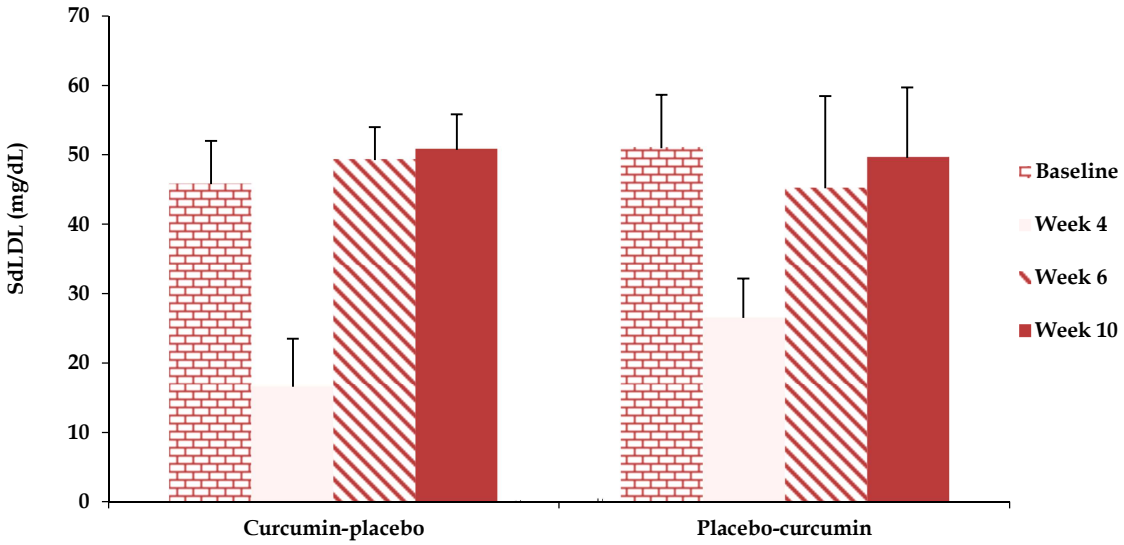

Figure 2. Serum small dense low-density lipoprotein (sdLDL) concentrations (mg/dl) at different time points of trial; Values are expressed as mean ± SEM. There was no effect of curcuminoids on serum sdLDL (P = 0.382, first carry-over effect; P = 0.262, second carry-over effect; P = 0.820, treatment effect);
SEM: Standard error of mean

Different mechanisms have been proposed for the atherogenicity of sdLDL.[27-30] According to Bjornheden et al., sdLDL is more readily taken up by arterial tissue because of easier transendothelial migration of smaller particles.[27] It has been reported that the prevalence of sdLDL is 5-10% in young men and women under 20 years old and around 30% in adult males.[31,32] The sdLDL-C/LDL-C in our trial exceeded these values and conformed to previous findings in obese individuals.[33,34]

Several lines of preclinical evidence have indicated the hypolipidemic effects of curcuminoids in different experimental models, for example, rats, rabbits, hamsters, and mice.[20] These effects were reported to be reductions in circulating levels of total cholesterol, LDL-C, triglycerides and free fatty acids, and increases in HDL-C.[20] Different mechanisms have been proposed for these hypolipidemic actions including inhibition of intestinal cholesterol absorption, inhibition of hepatic lipid biosynthesis, stimulation of bile secretion and modulation of the expression and/or activity of lipoprotein receptors.[20] In spite of these promising findings, hypolipidemic effects of curcuminoids have not been consistently reported in randomized controlled trials.[19,35-39] Taken together, the overall clinical findings on the effect of curcuminoids supplementation on LDL-C levels weighs in favor of lack of efficacy. The present findings on sdLDL are also in line with those previously found on LDL-cholesterol.[19,40]

Increasing evidence has suggested a link between

circulating triglycerides levels, as well as triglycerides content of LDL particles, with CHD risk.[41,42] In a recent report from the same trial, it was shown that curcuminoids supplementation is associated with a significant hypotriglyceridemic effect but not any change in the levels of total and LDL-C.[19] Interestingly, another recent trial by DiSilvestro et al. showed the same finding.[40] The lack of efficacy on the circulating levels of total cholesterol, LDL-C and sdLDL is unlikely to be due to the low-bioavailability of this compound as both of the above-mentioned trials used improved formulations of curcuminoids through co-administration with piperine,[19] or using lipidated form of curcuminoids in combination with absorption enhancing adjuvants.[40] Therefore, it is plausible that the positive cardio-protective and anti-atherogenic properties of curcuminoids are primarily due to an effect on triglyceride levels rather than LDL and its sub-fractions. This issue merits further investigation.

The lack of efficacy of curcuminoids in altering serum levels of sdLDL is unlikely to be attributable to the insufficient administered dose or trial duration as similar trials with the same durations were able to show the efficacy of curcuminoids on other CHD biomarkers, most importantly triglycerides, as mentioned above. There is evidence indicating down-regulation of genes involved in lipogenesis by curcuminoids.[20] Nevertheless, there has been as yet no evidence of the modulatory effect of curcuminoids on hepatic lipase, the main enzyme responsible for the conversion of large and medium LDL particles (LDL-I and LDL-II) to sdLDL. Furthermore, evidence regarding the impact of curcuminoids on activity of CETP is also lacking. CETP is another key enzyme responsible for the remodeling of LDL from large to smaller particles. There has been only one previous study showing the inhibitory effect of curcumin on CETP, but this study was conducted in LDL receptor knockout mice model that cannot be a true representative of clinical conditions.[43]

The main strength of the present study is that it was based on a robust placebo-controlled and cross-over design and conducted in the target population, not under concomitant lipid-lowering therapy. Therefore, many of the confounding factors that may generally affect lipid alterations were eliminated from the present trial. Second, this study is the first one to look at sdLDL changes following curcuminoids therapy. Aside from these strengths, a number of limitations need to be acknowledged for the present trial: First, this study was not primarily aimed to assess the impact of curcuminoids on serum sdLDL. Second, the composition of LDL was not investigated in this study. Recent data have shown that lipid composition of LDL particles plays a significant role in the atherogenicity of particles.[44]

Conclusion

In summary, results obtained from the current trial indicated no significant effect of curcuminoids supplementation on circulating levels of sdLDL. This finding may imply that beneficial cardiovascular effects of curcuminoids are exerted via mechanisms other than affecting LDL sub-fractions. Nevertheless, future studies are encouraged to explore the impact of curcuminoids on serum lipidome as well as triglyceride and fatty acid composition of lipoprotein species.

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Conflict of Interests

Authors have no conflict of interests.

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