Effects of Supplementation with Curcuminoids on Dyslipidemia in Obese Patients: A Randomized Crossover Trial

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Dyslipidemia is a leading risk factor for cardiovascular disease and is also a common feature of obesity. Curcumin is a bioactive phytochemical with well-known antioxidant, anti-inflammatory, and cardioprotective properties. The present study investigated the hypolipidemic activity of curcumin in obese individuals. Participants (n=30) were treated with curcuminoids $(1\,\mathrm{g/day})$, or placebo in a randomized, double-blind, placebo-controlled, crossover trial. Serum concentrations of total cholesterol, triglycerides, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol, together with anthropometric parameters and high-sensitivity C-reactive protein were measured before and after each treatment period. Anthropometric parameters including weight, BMI, waist circumference, hip circumference, arm circumference, and body fat remained statistically unchanged by the end of trial (p>0.05). As for the lipid profile parameters, serum triglycerides were significantly reduced following curcumin supplementation (p=0.009). However, curcuminoids were not found to affect serum levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and high-sensitivity C-reactive protein (p>0.05). In summary, the findings of the present study indicated that curcuminoid supplementation $(1\,\mathrm{g/day}$ for 30 days) leads to a significant reduction in serum triglycerides concentrations but do not have a significant influence on other lipid profile parameters as well as body mass index and body fat. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: obesity; hyperlipidemia; triglyceride; cholesterol; cardiovascular disease; C-reactive protein; body mass index.

INTRODUCTION

Obesity is becoming a major public health problem. It is also a major risk factor for development of diabetes, hyperlipidemia, and osteoarthritis (Rao *et al.*, 2001; Ridker *et al.*, 2001; Eckel, 1997, Eckel and Krauss, 1998; Seidell, 1998; Gaziano *et al.*, 2001; Groessl *et al.*, 2004). Based on a recent report, the prevalence of overweight and obesity in elderly subjects in the Razavi Khorasan province of Iran is 28.9 and 11.7%, respectively (Nematy *et al.*, 2009), and is at an approximate prevalence of 7.8 and 19.7% in male and female individuals aged 15–65 years (Azimi-Nezhad *et al.*, 2009). The prevalence of overweight and obesity are rising rapidly even in developing countries, and measures are therefore required to prevent the associated complications (Nematy *et al.*, 2009; Azimi-Nezhad *et al.*, 2009).

Curcuma longa L. is a perennial herb belonging to the ginger family that is cultivated extensively in south Asia. The underground rhizomes of this plant, commonly known as turmeric, are widely used for culinary and medicinal purposes (Shishodia *et al.*, 2005). Curcumin

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(diferulovlmethane; Fig. 1) is a polyphenolic compound and is the active ingredient of turmeric makes up 2-5% of the spice (Shishodia et al., 2005; Goel et al., 2008). Curcumin was first isolated in 1815, obtained in crystalline form in 1870, and ultimately identified as 1,6-heptadiene-3,5-dione-1,7-bis (4-hydroxy-3-methoxyphenyl)-(1E, 6E) or diferuloylmethane. In 1910, the feruloylmethane skeleton of curcumin was confirmed and synthesized by Lampe (1913). Curcumin is an orange-yellow crystalline powder that is insoluble in water and ether but soluble in ethanol, dimethylsulfoxide, and acetone (Goel et al., 2008). Turmeric is used as a spice, coloring agent in foods and textiles, and a treatment for a wide variety of ailments. It is widely used in traditional Indian medicine to cure biliary disorders, anorexia, cough, diabetic wounds, hepatic disorders, rheumatism, and sinusitis. Recent phase I clinical trials indicate that curcumin doses as high as 8 g/day could be tolerated with no side effects (Cheng et al., 2001).

In recent years, several potentially important biological properties for curcumin have been described including antioxidant, antiinflammatory, anti-thrombotic, and hepatoprotective actions (Naika *et al.*, 2004). Recent studies suggest that curcumin is a lipid-lowering compound that can significantly decrease the levels of total serum cholesterol and lipid peroxides in experimental animal models (Soudamini *et al.*, 1992; Srinivasan *et al.*, 2004; Manjunatha and Srinivasan, 2007). However, there

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Figure 1. Chemical structure of curcumin.

have been few clinical trials investigating the lipid lowering activity of curcumin (Soni and Kuttan, 1992; Ramirez Bosca *et al.*, 2000; Baum *et al.*, 2007), with no previous study specifically performed in obese individuals. The present study was undertaken to evaluate the hypolipidemic effects of curcumin in obese subjects.

MATERIALS AND METHODS

Subjects

Thirty subjects aged 18–65 years who were not originally taking lipid-lowering agents were recruited from the Lipid Clinics at the Ghaem Hospital (Mashhad, Iran). In addition to a history of not taking any lipid lowering drugs, other inclusion criteria were any of the following conditions [based on the NCEP-ATP III guidelines (Third Report of the National Cholesterol Education Program (NCEP), 2002)]: (1) patients with BMI \geq 30, (2) patients with < 2 risk factors (except diabetes mellitus) for coronary heart disease (CHD) and 160 mg/dL <LDL-C<190 mg/dL, or (3) patients with ≥ 2 risk factors (except diabetes mellitus) for coronary heart disease (CHD) and 130 mg/dL < LDL-C < 160 mg/dL. Cardiovascular risk factors were defined as age > 65 years, hypertension (defined as taking any anti-hypertensive medication; or systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg), diabetes mellitus (defined as fasting blood sugar (FBS) \geq 126 mg/dL), positive family history of cardiovascular disease, smoking, male sex, and obesity [defined as body mass index (BMI) \geq 30 kg/m²].

Exclusion criteria were systemic disease or history of systemic disease (such as lupus, kidney disease, diabetes mellitus), history of cardiovascular disease, BMI < 30, consumption of drug supplements within the 6 months and history of taking any lipid-lowering drug. Each subject gave informed written consent to participate in the study, which had previously been approved by the Mashhad University of Medical Sciences Ethics Committee. In addition, subjects were advised to continue their normal medication schedule.

Study design

This study was designed as a randomized double blind crossover trial in which each patient received curcuminoids or placebo and then crossed over to the alternate regimen. Each treatment period was 30 days and there was a 2-week wash-out interval between the regimens. The dose of curcuminoids and all other medication remained unchanged during the experimental period,

and the patients were advised not to change their lifestyle during the study. At the first visit, patients were randomized for one of two treatment regimens, 16 patients were provided with curcuminoids 1 g/day for 30 days and other 16 patients received a placebo for 30 days. Curcuminoids were administered in the form of C3 Complex® capsules (Sami Labs LTD, Bangalore, India) containing 500-mg curcuminoids plus 5-mg bioperine[®]. Bioperine[®] is an extract obtained from black pepper (Piper nigrum L.) or long pepper (Piper longum L.), and contains 95% piperine, which is a well-documented bioavailability enhancer. Placebo capsules used in the study were shape-matched and size-matched, and contained piperine (5 mg). After another 2-week washout period, patients crossed over to the other form of treatment (Fig. 2).

Anthropometric measurements

Anthropometric parameters including weight, height, BMI, waist circumference, arm circumference, and fat percentage were measured. Weight was measured with the subjects dressed in light clothing after an overnight fasting using a standard scale. BMI was calculated as weight (kg) divided by squared height (m²).

Blood sampling

Blood samples were collected four times for each subject (before and after starting each period). Blood samples for laboratory assays were obtained on the day of sampling after 12 h of fasting. Blood samples were collected in Vacutainer tubes and centrifuged at $10,000\,\mathrm{g}$ for $15\,\mathrm{min}$. After separation, aliquots of serum were frozen at $-80\,^\circ\mathrm{C}$ until analysis.

Routine biochemical analysis

A full fasted lipid profile comprising total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) was determined for each subject. Serum lipid concentrations were measured enzymatically with the use of commercial kits.

Statistical analysis

Values were expressed as means \pm SD. The comparison between pre-treatment and post-treatment values was performed using paired t-test or Wilcoxon signed-rank test for normally and non-normally distributed data, respectively. Data obtained from independent variables analyzed using Student's t-test (for those with normal distribution) or Mann–Whitney U test (for those with non-normal distribution). Categorical data were compared using chi-squared test. Mixed model analysis of variance for 2×2 crossover studies was fitted when assumption for normality were met. All analysis was performed with the Statistical Analysis Software (SAS; version 9.1). A two-sided p-value of <0.05 was considered statistically significant.

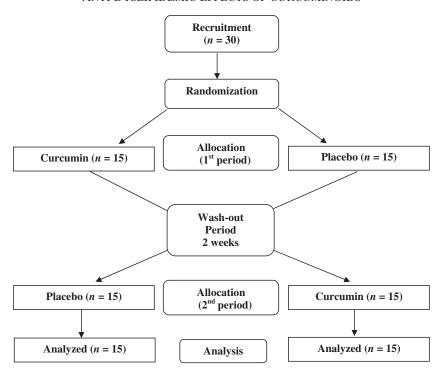


Figure 2. Flow chart of trial.

RESULTS

Demographic characteristics of the study population are summarized in Table 1. Table 2 shows the baseline and post-trial values of evaluated biochemical parameters.

Anthropometric parameters including weight, BMI, waist circumference, hip circumference, arm circumference, and body fat remained statistically unchanged by the end of trial (p > 0.05; Table 2). As for the lipid profile parameters, serum triglycerides were significantly reduced following curcumin supplementation (p = 0.009; Table 2). However, curcumin was not found to affect serum levels of total cholesterol, LDL-C and HDL-C (p > 0.05; Table 2). Serum hs-CRP concentrations were not significantly altered by the end of trial (p > 0.05; Table 2).

Table 1. Subject characteristics at baseline

| Sex (Female) | 83.3% |
|---------------------------|-------------------------------------------|
| Age (years) | 38.43 ± 10.84 (18–52) |
| Height (cm) | $158.62 \pm 7.82 \; (142 175)$ |
| Weight (kg) | 82.10 ± 11.58 (67.4–114.2) |
| Waist circumference (cm) | $106.85 \pm 11.58 \; (95.5 134.0)$ |
| Hip circumference (cm) | $114.79 \pm 7.62 \; (103.0 138.5)$ |
| Arm circumference (cm) | $33.81 \pm 2.56 \; (28.0 39.0)$ |
| Fat percentage (%) | $38.30 \pm 5.97 \; (23.5 – 47.9)$ |
| BMI (kg/m2) | $32.60 \pm 3.58 \; (25.6 42.3)$ |
| Total cholesterol (mg/dL) | $193.13 \pm 28.67 \; (135.0 – 251.0)$ |
| HDL-C (mg/dL) | $46.47 \pm 8.70 \; (27.0 63.0)$ |
| LDL-C (mg/dL) | $120.00 \pm 25.41 \; \text{(67.0-164.0)}$ |
| Triglycerides (mmol/L) | $115.97 \pm 46.09 \; (53.0 – 262.0)$ |
| Hs-CRP (mg/L) | $\textbf{8.56} \pm \textbf{2.59}$ |

All values are expressed as mean ± SD. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Curcumin was found to be safe and well-tolerated in study patients. Overall, there were few reports of adverse effects [constipation (n=2), diuresis (n=1), and increased volume and duration of menstrual blood loss (n=1)] following curcumin therapy. With respect to placebo, there was a single report of constipation and three reports of feeling bloated.

DISCUSSION

The results of the present study indicated that curcumin supplementation is associated with a significant reduction in serum triglyceride levels. However, curcumin did not cause a significant change in serum total cholesterol, LDL-C, HDL-C, or hs-CRP levels. BMI, weight, waist circumference, arm circumference, and body fat were not statistically changed, either.

There have been several reports investigating lipidlowering activity of curcumin in experimental animal studies. The study of Manjunatha and Srinivasan, (2007) indicated that curcumin does not significantly affect total cholesterol concentration, HDL-C, and triglycerides in hypercholesterolemic rats. In a similar study by Rao et al. (1970), no statistically significant difference in total serum cholesterol between control group and curcuminsupplemented groups was noted. Babu and Srinivasan, (1997) have reported that blood cholesterol was significantly lowered in diabetic animals maintained on 0.5% curcumin-containing diet. In addition, HDL-C was increased by curcumin by 25% in diabetic animals. A significant decrease in blood triglycerides were also brought about in diabetic animals maintained on curcumin diet.

With respect to clinical studies in man, there have been a number of reports with inconsistent findings. In a previous double-blind placebo-controlled trial by Baum

Table 2. Effect of curcumin supplementation on evaluated anthropometric and biochemical measures

| Age (years) Weight (kg) Waist circumference (cm) Hip circumference (cm) Arm circumference (cm) Placeb Arm circumference (cm) Placeb Fat percentage (%) BMI (kg/m2) Placeb Placeb Placeb Placeb Placeb Placeb Curcur Placeb Placeb Placeb Curcur Placeb Placeb Curcur Placeb Placeb Curcur Placeb Curcur | Curcumin-placebo Placebo-curcumin Curcumin-placebo Placebo-curcumin Curcumin-placebo | 15 | Pre-treatment | | | | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|----|----------------------------------|---------------------------------|----------------------------------|------------------|---------------|------------------|
| | umin-placebo bo-curcumin umin-placebo bo-curcumin umin-placebo umin-placebo | 15 | | Post-treatment | Pre-treatment | Post-treatment | Period effect | Treatment effect |
| _ | bo-curcumin Imin-placebo bo-curcumin Imin-placebo bo-curcumin Imin-placebo | | 39.0 ± 9.0 | | 1 | 1 | 1 | |
| _ | umin-placebo bo-curcumin umin-placebo bo-curcumin umin-placebo | 15 | 37.9 ± 12.7 | | 1 | • | • | , |
| | bo-curcumin umin-placebo bo-curcumin umin-placebo | 15 | 84.1 ± 13.5 | 84.3 ± 14.6 | 83.6 ± 15.1 | 82.9 ± 14.9 | 0.71 | 0.23 |
| | umin–placebo ibo–curcumin umin–placebo | 15 | 80.1 ± 9.3 | 78.7 ± 8.7 | $\textbf{78.6} \pm \textbf{9.2}$ | 78.3 ± 10.2 | | |
| | bo-curcumin umin-placebo | 15 | 109.2 ± 10.2 | 106.2 ± 11.5 | 103.1 ± 9.0 | 101.7 ± 9.4 | 0.01 | 0.82 |
| | umin-placebo | 15 | 104.5 ± 6.9 | 101.1 ± 6.4 | 98.6 ± 7.6 | 97.7 ± 5.5 | | |
| | | 15 | 116.4 ± 9.0 | 114.3 ± 8.6 | 113.6 ± 9.2 | 112.8 ± 9.6 | 0.19 | 0.78 |
| | Placebo-curcumin | 15 | 113.2 ± 5.8 | 111.3 ± 5.9 | 109.8 ± 5.2 | 108.5 ± 5.9 | | |
| | Curcumin-placebo | 15 | 34.6 ± 2.2 | 33.4 ± 2.8 | 33.3 ± 2.9 | 32.8 ± 2.8 | 0.35 | 0.97 |
| | Placebo-curcumin | 15 | 33.0 ± 2.7 | 32.1 ± 1.9 | 32.9 ± 2.6 | 32.4 ± 3.0 | | |
| | Curcumin-placebo | 15 | 40.2 ± 5.5 | 39.9 ± 5.5 | 40.0 ± 6.0 | 39.6 ± 6.1 | 0.95 | 0.88 |
| | Placebo-curcumin | 15 | $\textbf{36.4} \pm \textbf{6.0}$ | 36.0 ± 5.9 | 36.3 ± 6.2 | 36.0 ± 6.0 | | |
| | Curcumin-placebo | 15 | 33.4 ± 3.7 | 33.4 ± 4.4 | 33.2 ± 4.8 | 32.9 ± 7.8 | 0.61 | 0.21 |
| | Placebo-curcumin | 15 | 31.8 ± 3.4 | 31.2 ± 3.1 | 31.2 ± 3.3 | 31.0 ± 3.4 | | |
| | Curcumin-placebo | 15 | 195.6 ± 30.4 | 195.3 ± 30.7 | 191.0 ± 35.3 | 195.7 ± 33.7 | 0.89 | 0.30 |
| Placeb | Placebo-curcumin | 15 | 190.7 ± 27.7 | 192.0 ± 34.4 | 202.8 ± 27.2 | 204.5 ± 41.9 | | |
| LDL-C (mg/dL) Curcur | Curcumin-placebo | 15 | 119.7 ± 23.6 | 129.6 ± 26.4 | 118.9 ± 29.0 | 129.7 ± 30.3 | 0.65 | 0.99 |
| | Placebo-curcumin | 15 | 120.3 ± 27.9 | 119.4 ± 31.5 | 124.6 ± 27.9 | 130.9 ± 36.9 | | |
| HDL-C (mg/dL) Curcur | Curcumin-placebo | 15 | 46.3 ± 9.8 | 48.3 ± 8.1 | 47.9 ± 7.7 | 49.6 ± 9.6 | 0.87 | 0.83 |
| | Placebo-curcumin | 15 | $\textbf{46.6} \pm \textbf{7.8}$ | 46.3 ± 6.9 | 53.1 ± 9.3 | 52.3 ± 9.9 | | |
| Triglycerides (mg/dL) Curcur | Curcumin-placebo | 15 | 105.7 ± 30.2 | 95.1 ± 38.8 | 104.1 ± 46.6 | 100.9 ± 39.0 | 0.26 | *600.0 |
| Placeb | Placebo-curcumin | 15 | 126.2 ± 57.1 | 127.6 ± 46.6 | 120.7 ± 64.2 | 104.7 \pm 44.4 | | |
| Hs-CRP (mg/L) Curcur | Curcumin-placebo | 15 | 8.6 ± 2.6 | 8.6 ± 3.1 | 8.1 ± 4.0 | 7.2 ± 2.39 | 0.49 | 0.27 |
| Placeb | Placebo-curcumin | 15 | 8.5 ± 2.6 | $\textbf{7.7} \pm \textbf{2.4}$ | $\textbf{7.2} \pm \textbf{2.8}$ | 6.8 ± 2.4 | | |

All values are expressed as mean ± SD. LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C reactive protein.

et al. (2007), the effects of curcumin supplementation on serum lipid profile of 36 elderly subjects with Alzheimer's disease were examined. Subjects were administered curcumin at doses of 4 g/day or 1 g/day or placebo, for a period of 6 months. The results were similar to those of 3the present study and indicated no significant alteration in serum cholesterol, HDL-C, and LDL-C concentrations. However, no significant effect on serum triglycerides was observed in the aforementioned study. This discrepancy might be attributed to the smaller number of subjects compared with the current study, which might have affected the effect size. Another possible explanation for the negative findings of the latter study may be caused by the patient population studied. Unlike the present study, obesity was not among the inclusion criteria of the investigation by Baum and colleagues. Therefore, hypolipidemic effects of curcumin may not be elicited in such patients. Soni and Kuttan, (1992) in 10 healthy subjects showed that receiving 500 mg of curcumin per day for 7 days did significantly decrease serum total cholesterol (12%) and caused a statistically significant increase in serum HDL-C levels (29%). As mentioned, this study had a small sample size and limited follow-up period and thus lacked enough statistical power to detect the impact of curcumin on serum lipid profile. In contrast to these findings are the results of another study in which curcumin supplementation (10 mg twice daily for 28 days) lowered serum LDL-C and increased HDL-C levels in patients with atherosclerosis (Ramirez Bosca et al., 2000).

The antihypertriglyceridemic activity of curcumin that was observed in the present trial is most probably caused by the insulin sensitizing effects of this phytochemical (Jang et al., 2008; Na et al., 2011; Shehzad et al., 2011). There is a pile of evidence indicating an increased risk of insulin resistance syndrome and diabetes mellitus in obese individuals (Kahn et al., 2006). This increased risk is attributed to the pathophysiological alterations in the secretion of adipokines and inflammatory cytokines by the adipose tissue (Shehzad et al., 2011). Improvement of adipokine status together with antiinflammatory effects of curcumin are potential mechanisms, which might be responsible for its beneficial impacts in the mitigation of insulin resistance (Shehzad et al., 2011). In addition, there has been a multitude of evidence on the role of Jun c-Jun N terminus protein kinase (JNK) activation in the impairment of insulin responsiveness and pathogenesis of insulin resistance and obesity (Hirosumi *et al.*, 2002). An important mechanism through which curcumin exerts its insulin sensitizing effects is downregulation of JNK

phosphorylation and activity (Chen and Tan, 1998; Wang et al., 2009).

A strength of the present trial is its crossover design that allows each patient to serve as their own control and thereby eliminating inter-individual differences and associated bias. On the other hand, there are some limitations that might explain the contradictory findings of the present trial to some of the previous reports. First, the duration of follow-up in the present study was relatively short. It is possible that longer-term supplementation may be required to determine the real impact of curcumin on serum lipoprotein concentrations. Second, the impact of curcumin dose was not investigated in the current research. It would be useful to test higher doses of curcumin - which have been previously shown to be quite safe – for the same purpose. This becomes important when considering the low bioavailability of curcumin. Third, more detailed studies are required to assess the dietary changes during the course of trial in order to normalize dietary intake of fats between case and control groups. Although a crossover design compensates for this problem to some extent, it does not completely rule out the need for dietary control.

CONCLUSION

In summary, the findings of the present study indicated that curcuminoid supplementation (1 g/day for 30 days) leads to a significant reduction in serum triglyceride concentrations but does not have a significant influence on serum total cholesterol, LDL-C, HDL-C, and hs-CRP concentrations, nor on BMI and body fat. Further larger-scale trials with extended follow-up durations are warranted to clarify curcumin's effects on lipid profile.

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Conflict of Interest

The authors have no conflict of interests to declare.

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