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Curcuminoids modify lipid profile in type 2 diabetes mellitus: A randomized controlled trial

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ABSTRACT

Background: Type 2 diabetes (T2D) is an established risk factor for cardiovascular disease (CVD) and is associated with disturbed metabolism of lipids and lipoproteins. Curcuminoids are natural products with anti-diabetic and lipid-modifying actions but their efficacy in improving dyslipidemia in diabetic individuals has not been sufficiently studied.

Objective: To investigate the efficacy of supplementation with curcuminoids, plus piperine as an absorption enhancer, in improving serum lipids in patients with T2D.

Methods: In this 12-week randomized double-blind placebo-controlled trial, subjects with T2D (n = 118) were assigned to curcuminoids (1000 mg/day plus piperine 10 mg/day) or placebo plus standard of care for T2D. Serum concentrations of lipids including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), lipoprotein(a) [Lp(a)], and non-HDL-C were determined at baseline and at the end of trial.

Results: Between-group comparison of change in the study parameters revealed significant reductions in serum levels of TC (−21.86 ± 25.78 versus −17.06 ± 41.51, respectively; $p = 0.023$), non-HDL-C (−23.42 ± 25.13 versus −16.84 ± 41.42, respectively; $p = 0.014$) and Lp(a) (−1.50 ± 1.61 versus −0.34 ± 1.73, respectively; $p = 0.001$) and elevations in serum HDL-C levels (1.56 ± 4.25 versus −0.22 ± 4.62, respectively; $p = 0.048$) in the curcuminoids group as compared with the placebo group ($p < 0.05$). Serum TG and LDL-C changes did not show any significant difference between the study groups ($p > 0.05$).

Conclusion: Curcuminoids supplementation can reduce serum levels of atherogenic lipid indices including non-HDL-C and Lp(a). Therefore, curcuminoids supplementation could contribute to a reduced risk of cardiovascular events in dyslipidemic patients with T2D.

1. Introduction

Curcuminoids are bioactive phenols responsible for the yellow color of turmeric (*Curcuma longa* Linn.), a spice that has been used throughout the history in South Asian and Middle Eastern cuisine. Curcuminoids comprise of curcumin, demethoxycurcumin and bisdemethoxycurcumin.[1] It has been shown that curcuminoids have different beneficial pharmacological effects.[2–6] For instance, a 9-month intervention with 1500 mg/day of curcumin in a prediabetic population significantly lowered the number individuals who developed type 2 diabetes mellitus (T2DM).[7] Curcuminoids have also glucose-lowering effects in patients with established T2DM.[8] On the other hand, curcuminoids have been reported to have many antiatherogenic properties such as antiinflammatory and antioxidant activities.[9–13] Curcuminoids lower circulating concentrations of pro-inflammatory mediators such as TNF-α, IL-1, IL-6, IL-8, adhesion molecules (ICAM, VCAM) and C-reactive protein (CRP).[14–20] Curcuminoids have shown beneficial effects in lowering serum lipids but the evidence, particularly in high-risk

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populations, is still insuffieint.[21–25] For instance, low doses of 80 mg/day were shown to reduce plasma trigylcerides (TG) in 19 healthy middle aged subjects when compared with 19 subjects on placebo, while high doses of 1000 mg/day of curcumin reduced plasma TG in 30 obese subjects but did not affect serum levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C).[26,27] The same dose was reported to reduce serum TC, LDL-C, non-HDL-C and elevated serum HDL-C in 50 patients with metabolic syndrome who were treated with standard of care.[28] In patients with acute coronary syndrome curcumin, in very low doses of 15, 30 and 60 mg/day as adjunct therapy, reduced TC and LDL-C and increased HDL-C levels with lower doses showing higher efficacy.[29] Curcuminoids were also shown to reduce TC and LDL-C and increase HDL-C levels in patients with nonalcoholic fatty liver disease (NAFLD).[22,30]

The oral absorption of curcumin is low due to its hydrophobic nature, and its metabolism and sytemic elimination are rapid, leading to a low systemic bioavailability. This issuehas been resolved by using several formulation improvements, such as coadministration with absorption-enhancing adjuvants such as piperine.[31]

The effects of curcuminoids on plasma lipoproteins still remain controversial and a recently published meta-analysis could not prove any effect of curcumin supplementation on serum TC, LDL-C, triglycerides and HDL-C levels in heterogeneous populations.[32] The aim of this study was therefore to evaluate the efficacy of curcuminoids plus piperine on serum lipoproteins in patients with type 2 diabetes mellitus who are by definition at a high or very high risk for atherosclerotic cardiovascular disease (CVD).[33]

2. Materials and methods

2.1. Subjects

Adult subjects aged 18–65 years were recruited from those referring to the Diabetes Clinic of the Baqiyatallah Hospital (Tehran, Iran). The inclusion criteria were diagnosis of T2DM based on fasting plasma glucose (FPG) ≥ 126 mg/dL, glycated hemoglobin (HbA1C) ≥ 6.5%, or the use of anti-diabetic treatments. Exclusion criteria were pregnancy or breastfeeding, lack of possibility to give an informed consent, participation in a concomitant trial, presence of malignancies, chronic liver disease (alanine aminotransferase levels three times upper the limit of normal value range), renal failure (serum creatinine ≥ 2.0 mg/dL or being on dialysis), chronic inflammatory diseases such as rheumatoid arthritis and acute infections, endocrine diseases other than T2DM (e.g. hypothyroidism or hyperthyroidism), obsessive compulsive disorder, hyperglycemia due to secondary causes, receiving hormone therapy or other herbal medicines, hypersensitivity to the study medication, and lack of compliance with the study medication.

2.2. Study design

This study was designed as a randomized double-blind placebo-controlled trial with a parallel-group design and performed between June 22, 2015 and April 20, 2016. Subjects who met the mentioned inclusion criteria (n = 118) were randomly allocated to either curcuminoids (curcumin C3 Complex®, Sami Labs LTD, Bangalore, India) or placebo for a period of 12 weeks. Curcuminoid and placebo capsules were matched in shape, size and color, and the color of placebo was matched to that of curcuminoid powder. To enhance the oral bioavailability of curcuminoids, 5 mg piperine (Bioperine®; Sami Labs LTD, Bangalore, India) was added to each 500 mg curcuminoids capsule. C3 Complex® preparation that was used in the present study contained the three major curcuminoids including curcumin, demethoxycurcumin and bisdemethoxycurcumin in a patented ratio.

The study protocol was approved by the Ethics Committee at the Baqiyatallah University of Medical Sciences and registered in the Iranian Registry of Clinical Trials (code: IRCT201505301165N4). Written informed consent was obtained from all individuals.

2.3. Blood sampling and measurements

Overnight fasting blood samples were collected at baseline and at the end of the study. The samples were allowed to clot for about 30 min and then centrifuged at 750*g* for 10 min to obtain serum. Serum samples were aliquoted and frozen at −80 °C until measurements. Weight was measured with the subjects dressed in light clothing after an overnight fasting using a standard scale. Anthropometric indices were measured as previously described. Serum concentrations of total cholesterol, LDL-C, HDL-C and triglycerides were measured using routine enzymatic methods with commercial kits. Serum levels of lipoprotein (a) [Lp(a)] were measured using immunoassay. Serum non-HDL-C concentrations were calculated by subtracting HDL-C from total cholesterol.

2.4. Statistical analysis

Statistical analyses were performed using the IBM SPSS Statistics for Windows Version 20.0 (IBM Corp., Armonk, NY, USA). Normal distribution of continuous variables was checked using Kolmogorov-Smirnov test. Data were expressed as mean ± SD or median (interquartile range) for normally and non-normally distributed data, respectively. Within-group comparisons were performed using paired samples *t*-test or Wilcoxon signed-ranks test for normally and non-normally distributed data, respectively. Between-group comparisons were performed using independent samples *t*-test or Mann-Whitney *U* test for normally and non-normally distributed data, respectively. Comparison of categorical variables between the groups was performed using Chi-square test. In case of significant difference in baseline values, adjustment was made using univariate analysis of covariance (ANCOVA) and general linear model.

3. Results

A total of 100 subjects (50 in each group) completed the 12-week period of trial. Drop-out rate (18 patients) did not significantly differ between the groups (Fig. 1). During the trial, there was no report of any severe side effect, suggesting the safety of the administered combination.

Baseline parameters of the study groups are shown in Table 1. The serum levels of TC, TG, HDL-C, non-HDL-C and Lp(a) ($p > 0.05$) were comparable between the groups. However, baseline values of BMI ($p = 0.047$) and LDL-C ($p = 0.010$) were significantly lower in the curcuminoids group.

Within-group comparisons showed significant reductions in weight ($pn < 0.001$) and BMI ($p < 0.001$) in the curcuminoids group while these parameters increased by the end of trial in the placebo group ($p = 0.020$ for weight and $p = 0.023$ for BMI). With respect to the lipid profile, significant reductions in TC, TG, LDL-C and non-HDL-C were observed in both groups. However, reduction of serum Lp(a) and increase in HDL-C concentrations were only observed in the curcuminoids group (Table 2).

Between-group comparison of change in the study parameters revealed reductions in weight (−1.44 ± 1.58 versus 0.70 ± 2.05 in the curcuminoids and placebo group, respectively; $p < 0.001$), BMI (−0.49 ± 0.52 versus 0.24 ± 0.73; $p < 0.001$) and serum levels of TC (−21.86 ± 25.78 versus −17.06 ± 41.51; $p = 0.023$), non-HDL-C (−23.42 ± 25.13 versus −16.84 ± 41.42; $p = 0.014$) and Lp(a) (−1.50 ± 1.61 versus −0.34 ± 1.73; $p = 0.001$) and elevations in serum LDL-C (−8.22 ± 13.94 versus −30.16 ± 45.40; $p = 0.002$) and HDL-C (1.56 ± 4.25 versus −0.22 ± 4.62; $p = 0.048$) levels in the curcuminoids group as compared with the placebo group. However, when post-supplementation serum leves of LDL-C or changes in serum

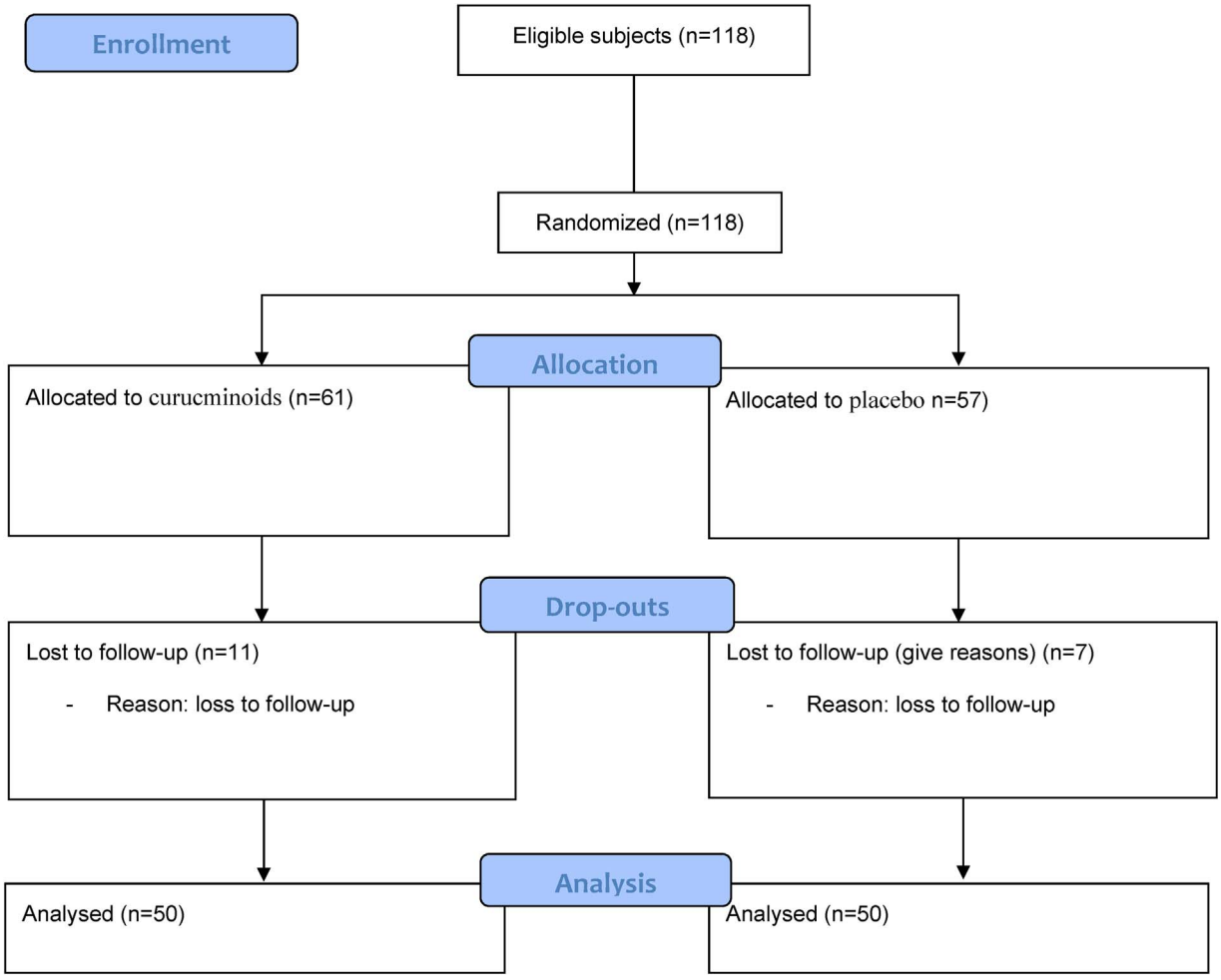

Fig. 1. Flow diagram of the trial.

Table 1
Clinical and biochemical features of the study groups at baseline.

	Curcuminoids	Placebo	*p*-Value
Gender (male/female)	25/25	26/24	1.00
Age (y)	43 ± 8	41 ± 7	0.190
Height (cm)	171.14 ± 6.65	168.78 ± 7.31	0.095
Weight (kg)	77.66 ± 7.37	77.9 ± 6.77	0.866
BMI (kg/m^2)	26.53 ± 2.32	27.33 ± 1.58	0.047
TC (mg/dL)	217.34 ± 41.60	231.04 ± 70.95	0.383
TG (mg/dL)	229.78 ± 81.84	207.62 ± 54.63	0.293
LDL-C (mg/dL)	169.16 ± 30.77	199.06 ± 54.49	0.010
HDL-C (mg/dL)	40.86 ± 5.41	39.46 ± 6.09	0.227
Non-HDL-C (mg/dL)	176.48 ± 42.26	191.58 ± 69.89	0.327
Lp(a) (mg/dL)	9.30 ± 1.84	9.46 ± 1.83	0.664

Values are expressed as mean ± SD. BMI: body mass index; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides; Lp(a): lipoprotein(a).

LDL-C levels were adjusted for baseline values, there was no difference between the study groups ($p > 0.05$). Serum TG changes (-24.30 ± 38.40 versus -20.56 ± 38.81; $p = 0.406$) did not show any significant difference between the study groups ($p > 0.05$). When the statistical comparisons were stratified according to gender, improvements in serum Lp(a) were significant after curcuminoids supplementation in both males and females (Table 3).

4. Discussion

Natural products have attracted increasing attention for the manegemnt of dyslipidemias and associated cardiometabolic diseases.[34–36] The results of this randomized double-blind placebo-controlled trial suggest that treatment of patients with T2DM with curcuminoid plus piperine for 12 weeks causes reduction of serum Lp(a) and an increase in HDL-C concentrations when compared with placebo group while there were no significant changes between these two groups in other lipoproteins. There was a significant decrease in serum levels of TC, LDL-C and TG in both groups but this, at least in part, can be explained by better control of the patients and most probably their better adherence to the lifestyle changes. However, it is very important to emphasize that there was a significant decrease in Lp(a), and non-HDL-C both in women and in men, and an increase in HDL-C in those T2DM patients who were taking curcuminoids which could not be seen in placebo group. Although elevated Lp(a) has been considered as an important risk factor for premature atherosclerotic CVD for quite a long time independently of LDL-C and non-HDL-C levels,[37,38] until very recently, the possibilities of influencing Lp(a) were extremely limited.[33] The effects of statins and fibrates on Lp(a) are controversial,[39] while niacin which could significantly reduce Lp(a) is no longer approved in Europe.[40] This happened following the results of HPS2-THRIVE and AIM-HIGH trials which reported that niacin plus laropiprant, or niacin alone in combination with statin therapy, failed to reduce the rate of major CVD events versus statin therapy alone, but increased the risk of serious adverse events.[41] At the moment, it seems that the only substances which can decrease Lp(a) substantially are PCSK9 inhibitors which appeared very recently on the market an.[42–44] It has been shown that some non-lipid-lowering substances are also able to reduce plasma Lp(a) concentrations, but further evidence from randomized controlled

Table 2
Comparisons of clinical and biochemical parameters before and after intervention in the study groups.

	Curcuminoids			Placebo		
	Before	After	*p*-Value	Before	After	*p*-Value
Weight(kg)	77.66 ± 7.37	76.22 ± 7.38	< 0.001	77.9 ± 6.77	78.60 ± 7.12	0.020
BMI(kg/m^2)	26.53 ± 2.32	26.04 ± 2.35	< 0.001	27.33 ± 1.58	27.57 ± 1.63	0.023
TC (mg/dL)	217.34 ± 41.60	195.48 ± 33.39	< 0.001	231.04 ± 70.95	213.98 ± 55.12	0.005
TG (mg/dL)	229.78 ± 81.84	205.48 ± 64.52	< 0.001	207.62 ± 54.63	187.06 ± 44.34	< 0.001
LDL-C (mg/dL)	169.16 ± 30.77	160.94 ± 28.32	< 0.001	199.06 ± 54.49	168.90 ± 29.91	< 0.001
HDL-C (mg/dL)	40.86 ± 5.41	42.42 ± 4.33	0.012	39.46 ± 6.09	39.24 ± 5.93	0.696
Non-HDL-C (mg/dL)	176.48 ± 42.26	153.06 ± 33.72	< 0.001	191.58 ± 69.89	174.74 ± 54.64	0.006
Lp(a) (mg/dL)	9.30 ± 1.84	7.80 ± 1.62	< 0.001	9.46 ± 1.83	9.12 ± 1.22	0.135

Values are expressed as mean ± SD. BMI: body mass index; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides; Lp(a): lipoprotein(a).

Table 3
Comparison of changes in biochemical indices between the study groups in each gender.

	Males			Females		
	Curcuminoids	Placebo	*p*-Value	Curcuminoids	Placebo	*p*-Value
TC (mg/dL)	−17.04 ± 16.53	−24.15 ± 44.46	0.220	−26.68 ± 32.18	−9.37 ± 37.47	0.089
LDL-C (mg/dL)	−6.96 ± 12.72	−34.96 ± 45.98	0.006	−9.48 ± 15.22	−24.96 ± 45.15	0.122
HDL-C (mg/dL)	2.40 ± 3.87	0.19 ± 5.27	0.096	0.72 ± 4.51	−0.67 ± 3.86	0.255
Non-HDL-C (mg/dL)	−19.44 ± 16.02	−24.35 ± 43.91	0.597	−27.40 ± 31.62	−8.71 ± 37.77	0.066
TG (mg/dL)	−23.68 ± 34.96	−20.54 ± 36.41	0.755	−24.92 ± 42.29	−20.58 ± 42.05	0.721
Lp(a) (mg/dL)	−1.48 ± 1.26	−0.54 ± 1.79	0.035	−1.52 ± 1.92	−0.12 ± 1.68	0.009

Values are expressed as mean ± SD. TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides; Lp(a): lipoprotein (a).

trials is still required.[45–48] Hence, this finding that curcuminoids as naturally occurring dietary supplements can decrease elevated Lp(a) in patients with T2DM is very important since such supplements are becoming more and more popular and attractive to the patients.

The finding that curcuminoids can elevate low HDL-C serum levels in patients with T2DM is also important because the problem with increasing HDL-C is much more complex than lowering LDL-C. Although HDL-C is, according to the guidelines, not recommended as a target for treatment,[49] it is well known that low HDL-C is a risk factor for CVD. Low HDL-C can be increased by lifestyle changes such as reducing intake of dietary trans fats, increasing habitual physical activity, reducing excessive body weight, reducing dietary carbohydrates and replacing them with unsaturated fat and consuming very modest quantities of alcohol. However, when drugs are concerned, it is well known that statins increase HDL-C only very modestly and the influence of these drugs is not completely understood while the efficacy of fibrates to increase HDL-C may be attenuated in people with T2DM.[50,51] A number of clinical studies have yielded disappointing results about the therapeutic benefit of elevating low serum HDL-C with different new drugs. The most important reason is probably that it is not the quantity of HDL-C that matters but HDL dysfunctionality, particularly in some conditions like T2DM,[52] contributes to elevated risk of CVD. The results of this study indicating an increase of HDL-C caused by curcuminoids fit well with the idea that protective properties of curcumin might influence HDL functionality.[25]

5. Conclusion

The results of this randomized double-blind placebo-controlled trial suggest that treatment of patients with T2DM with curcuminoid plus piperine after 12 weeks can cause reduction of serum Lp(a) and increase in HDL-C concentrations when compared with placebo group while there were no significant changes between these two groups in terms of other lipoproteins. This is important since until very recently, the possibilities of influencing Lp(a) were extremely limited. Therefore, a natural product such as curcuminoids plus piperine might be a useful supplement in treating dyslipidaemias in patients with T2DM.

Conflict of interests

Muhammed Majeed is the Founder & Chairman of Sabinsa Corporation and Sami Labs Limited.

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