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Clinical trial

The effect of green coffee extract supplementation on serum oxidized LDL cholesterol and total antioxidant capacity in patients with dyslipidemia: A randomized, double-blind, placebo-controlled trial

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ABSTRACT

Introduction: Previous studies on laboratory animals have evaluated the effects of CGA (chlorogenic acids) rather than GCBE (green coffee bean extract), and few studies have been conducted on human models. Thus, the purpose of the present study was to assess the effect of GCBE consumption on serum oxidized LDL-cholesterol (OX-LDL) and total antioxidant capacity (TAC) on patients with dyslipidemia.

Method: In this randomized, placebo-controlled, clinical trial, 70 male participants (age range 30–55 years) were assigned from the outpatient clinic of Arvand Petrochemical Company in Mah-shahr, Ahwaz, Iran to use 800 mg/day GCBE supplements or placebo for 8 weeks. Serum TAC and OX-LDL were determined by enzyme-linked immunosorbent assay.

Results: Compared with the placebo, GCBE intake led to a significant reduction in OX-LDL (−31.18 ng/ml) (P-value = < 0.001) and a significant increase in TAC (71.73 μmol/l) concentration (P-value = 0.029). In the intervention group, GCBE supplementation resulted in a significant reduction in Oxidized LDL of −16.08 ± 33.30 (ng/ml) (P-value = 0.006), compared to baseline.

Conclusions: The current trial showed that the intake of 800 mg per day of GCBE may have favorable effects on TAC, and OX-LDL in patients with dyslipidemia. However, further studies are required to confirm the veracity of these results.

1. Introduction

Non-communicable diseases (NCD), including cardiovascular diseases (CVD), cancer and diabetes are among the leading causes of disability and mortality, globally [1]. For example, CVD account for 80% of all NCD deaths in the world [2]. Dyslipidemia, hypertension, hyperglycemia, abdominal obesity, diet factors, lack of physical activity and smoking are considered to be the main risk factors for CVD [3–5]. Moreover, oxidative stress and inflammation are reportedly linked with mortality in cardiovascular diseases; in addition, the activity of antioxidant enzymes and non-enzyme antioxidants with total antioxidant capacity as a predictor of coronary artery disease has been reported [6]. Dyslipidemia is a disease characterized by various disorders in the lipid profile that increase the serum concentrations of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG), and decrease the serum high-density lipoprotein cholesterol (HDL-C) levels [7]. The role of oxidative stress in the development and progression of CVD is well-recognized, due to its involvement in the pathogenesis of dyslipidemia and atherosclerosis, and attributed to oxidized LDL-C, which is derived from LDL oxidation by various processes [8]. Empirical evidence has demonstrated that dyslipidemia is a preliminary and important modifiable risk factor for CVD, and successfully

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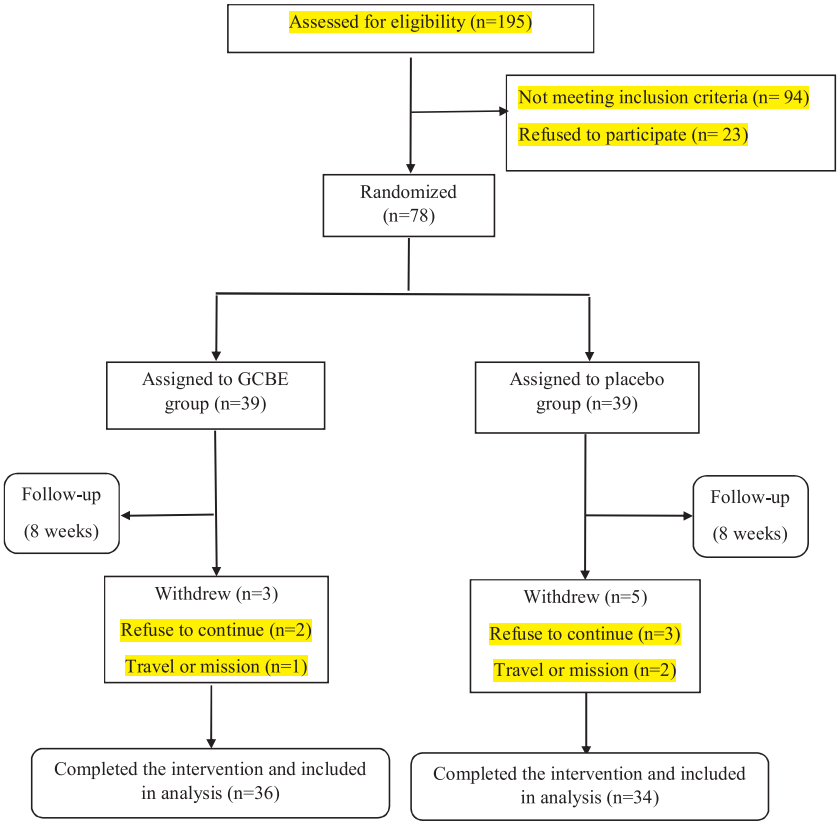

Fig. 1. Flow diagram of participant recruitment.

managing serum lipids concentrations can, conceivably, reduce the mortality rate of CVD [9,10]. Moreover, it has been shown that atherosclerosis may be improved by reducing serum LDL oxidized concentrations, even in the presence of high concentration of TG and LDL [11]. Lifestyle interventions and drug therapy are two major approaches to the treatment of dyslipidemia and, according to the latest American Heart Association guidelines, approaches to prevent CVD may also include healthy diet pattern, controlling weight, and maintaining lipid profile and blood pressure in a normal range [12]. Several epidemiologic studies have shown that the intake of food rich in antioxidants, such as vitamins (A, C, and E) and polyphenols can reduce deaths attributed to CVD [13,14]. Therefore, antioxidant intake and the effect of the nutritional supplementation on CVD is receiving growing, contemporary interest. Polyphenols are a major group of antioxidants that are extensively dispersed in foods such as coffee, apples, tomatoes, chocolate and tea. Green coffee bean extract (GCBE) is rich in polyphenols that promote defensive factors against chronic diseases initiated by oxidative stress [15]. Phenolic compounds with antioxidant characteristics are found abundantly within GCBE as a family of esters formed by several hydroxycinnamic acids (caffeic, ferulic and coumaric acids) and quinic acid, collectively known as chlorogenic acids (CGA) [16]. The anti-inflammatory and antioxidant features, along with anticarcinogenic characteristics of CGA and GCBE may play an important role in prevention and treatment of various chronic diseases, such as obesity, type 2 diabetes, cardiovascular dysfunction and cancers. Various animal studies have indicated the ameliorating effects of GCBE supplementation on chronic diseases such as hyperlipidemia, hypertension, diabetes and obesity [17–19]. Moreover, it has also been demonstrated, in laboratory animals, that CGA are among of the most effective constituents of green coffee and can decrease Fasting Blood Sugar (FBS) [20], Hemoglobin-A1c (HbA1c) [20], TG, TC, LDL-C and OX-LDL [21,22]. **S**ome human studies have demonstrated the beneficial effects of GCBE and CGA supplementation on blood pressure [23,24], lipid profile [25], body weight, body mass, fat mass indices [24,25] and serum levels of FBS [24]. In addition, CGA have been asserted capable of increasing total antioxidant capacity (TAC) [26,27], and decreasing some inflammatory biomarkers [27,28]. Previous studies have evaluated the effects of CGA, rather than GCBE, in laboratory animals, and few studies have been conducted on humans. Furthermore, no interventional study has been conducted investigating how GCBE supplementation effects patients with dyslipidemia. It is essential to explore potential efficacious treatments for dyslipidemia, particularly if it can help he prevention of cardiovascular diseases. The purpose of the present study was to assess the effect of GCBE consumption on serum OX-LDL and TAC in patients with dyslipidemia.

2. Material and methods

2.1. Study design

The present study was designed as a randomized, double-blind, parallel, placebo-controlled clinical trial. This study was conducted according to the principals of the Declaration of Helsinki and the study protocol was approved by the ethics committee of Ahvaz Jundishapur University of Medical Sciences (No. IR.AJUMS.REC.1396.899). This trial was also registered in the Iranian Registry of Clinical Trials (registration number: IRCT20180128038540N1). Written informed consent to participate in this study was provided by all of the volunteers and participants were informed about the aims and procedures prior to study commencement. A questionnaire regarding history of chronic disease, smoking status, demographic data, drug and dietary supplement history, prescribed medication and food habits was completed during participant interviews at the beginning of the study.

2.2. Study participants

In this clinical trial, a total of 78 adult men with new diagnosis of dyslipidemia were included in the randomization process (Fig. 1). Patients with dyslipidemia were recruited from the outpatient clinic of Arvand Petrochemical Company in Mah-shahr, Ahwaz, Iran. All participants were male because most employees were male, and therefore out of the operational control of the study. Disease status was confirmed according to the findings of an initial blood lipid profile test.

3. Sample size and power

We used the standard formula suggested for parallel clinical trials $n = [(Z_{\alpha/2} + Z_{1-\beta})^2 \times (2\ S^2)]/\ (\mu_1 - \mu_2)^2$ and $S^2 = ()n_1\text{-}1)S_1{}^2 + (n_2\text{-}1)S_2{}^2)/\ n_1 + n_2\ \text{-}2$ for estimating sample size by considering the type 1 error (α) of 0.05 and type 2 error (β) of 0.20 (power = 80%) [29]. Based on a previous study on oxidized low density lipoprotein, standard deviations were obtained (SD1 = 35.4 for control and SD2 = 25.71 for intervention group) [30]. With a forecast of 10–15 units of change in mean oxidized low density lipoprotein based on the previous study [31], the final sample size was determined to be 68 participants (34 per group).

3.1. Inclusion and exclusion criteria

Eligible patients were employees at Arvand Petrochemical Company, and were diagnosed with dyslipidemia if they satisfied 2 or more of these disorders: total cholesterol > 200 mg/dl, triglyceride > 150 mg/dl, LDL-C > 130 mg/dl, HDL-C < 40 mg/dl [7], did not consume any chemical or herbal medicine that might affect the blood glucose level and lipid profile and not having cancer, cardiovascular diseases, endocrine, liver or kidney dysfunction. Patients were excluded for the following reasons: coffee intolerance, coffee addiction, recent weight gain or weight loss, vegetarian diet and consumption of any antioxidant or dietary supplement in the 6 months preceding the beginning of the trial.

3.2. Intervention

A total of 78 dyslipidemic adult men were randomized, by random number tables, into an intervention or a control group. Participants in the intervention and control groups received either an oral dose of GCBE or placebo capsules (manufactured by Sabzdaru Co, Isfahan, Iran) twice per day, half an hour before lunch and dinner, respectively. Each GCBE capsule contained 400 mg of decaffeinated GCBE with 50% chlorogenic acid and each placebo capsule contained 400 mg of starch. Both the GCBE and the placebo capsules were identical in shape, color and size. The duration of the trial was 8 weeks. The dosage of GCBE and intervention period have been verified according to previous studies [32,33]. We contacted subjects weekly to ensure they followed the supplementation procedure.

3.3. Dietary intake assessment

All participants were advised not to change their dietary intake and physical activity during the study. Dietary intake, including total energy, fiber, fat, carbohydrate, and protein was evaluated by using 3-day validated food recall questionnaire (2 weekdays and 1 weekend day) for all participants at the beginning and the end of study. Energy and dietary nutrient content were calculated from the Iranian National Food Composition Tables [34], using modified nutritionist IV software (version 3.5.2, First DataBank; Hearst Corp, Sun Bruno, CA, USA).

3.4. Physical activity and anthropometric assessments

We used the International Physical Activity Questionnaire (IPAQ) [35] for assessing physical activity level at baseline and at the end of intervention. The participants were clustered into low, moderate, and high physical activity level. Weight, waist circumference, and fat mass of the participants were assessed, and BMI was computed at the beginning and at the end of trial. Height was determined, without shoes, using standard procedures and a tape measure with precision of 0.5 cm at baseline. Weight was recorded, with minimal clothing and barefoot, using a digital scale (SECA, Hamburg, Germany) to the nearest 0.1 kg. BMI was calculated as weight (kg) divided by height in square meters. Waist circumference (WC) was measured using a tape measure with precision of 0.5 cm at the midpoint between the last rib and iliac crest, without any pressure applied to the body surface. Fat mass was assessed via the bioelectrical impedance analysis (BIA) method using a body composition analyzer (OMRON, BF-511, Healthcare Co; Kyoto, Japan).

3.5. Laboratory assessment

Fasting blood samples (10 ml) from all subjects were obtained after a 12-h overnight fast, at the beginning and end of the 8 weeks. The samples were centrifuged at 3000 rpm for 10 min to prepare serum and then stored at −80 °C until analysis. Serum total antioxidant capacity (TAC) and oxidized LDL-cholesterol (OX-LDL) were determined by enzyme-linked immunosorbent assay using ELISA kits (Zellbio Gmbh, Ulm, Germany).

3.6. Statistical analyses

All statistical analyses were conducted with SPSS software, version 22 (SPSS Inc., Chicago, IL, USA). Normal distribution of all variables was assessed using Kolmogorov-Smirnov test. All data were presented as mean ± SD. Chi-square test was applied to compare qualitative variables between the trial groups. Paired-samples t-tests were used to compare differences pre and post intervention within each group. The means of variables between groups were compared using both independent-samples t-tests and ANCOVA in the adjusted models. A p-value < 0.5 was considered significant.

4. Results

Among the 78 dyslipidemic patients who participated in the study, 3 patients in the intervention group and 5 patients in the control group, respectively, withdrew from the study, leaving 70 participants included in the final analysis (Fig. 1). Patients withdrew due to personal reasons and/or travel commitments. Baseline characteristics of the participants in study are shown in Table 1. At baseline, Age, BMI, Weight, Waist circumference, OX-LDL, and TAC were not significantly different between groups. Changes in Oxidized LDL, and TAC after GCBE supplementation are indicated in Table 2. Compared with the placebo, GCBE intake led to a significant decline in OX-LDL (ng/ml) (P-value[a] = < 0.001) and a significant rise in TAC (μmol/l) concentration (P-value[a] = 0.029). In the intervention group GCBE supplementation resulted in a significant reduction in Oxidized LDL of -16.08 ± 33.30 (ng/ml) compared to baseline. In addition, within-group comparisons also showed that the mean concentration of TAC significantly increased post-trial in the intervention group (mean difference: 130.55 ± 134.75 (μmol/l), p < 0.001) and control group (mean difference: 58.824 ± 83.40 (μmol/l), p < 0.001).

Moreover, in the intervention group, weight (kg) (from 92.46 ± 15.2 to 91.82 ± 15.1, p = 0.009), BMI (kg/m) (from 26.40 ± 4.3 to 26.21 ± 4.3, p = 0.009), and mean visceral fat (%) (from 13.3 ± 4.4 to 12.53 ± 4.2, p = 0.018) reduced significantly. However, there were no significant changes in anthropometric indices in the placebo groups (the data are not shown in the table).

5. Discussion

Results of the present study indicated that supplementation with

Table 1
General characteristics of patients with dyslipidemia at the baseline.

Variables	Entire Cohort (n = 70)	Intervention (n = 36)	Control (n = 34)	P_value
Age(years)	39.18 ± 6.09	39.85 ± 6.46	38.49 ± 5.69	0.340
BMI(kg/m2)	26.13 ± 3.65	26.31 ± 4.19	25.95 ± 3.04	0.666
Weight(kg)	91.50 ± 13.37	92.16 ± 14.83	90.83 ± 11.85	0.669
Waist circumference)cm)	104.92 ± 9.30	104.39 ± 10.41	105.45 ± 8.10	0.623
Oxidized LDL(ng/ml)	64.56 ± 74.52	63.82 ± 69.89	65.35 ± 80.18	0.933
TAC (μmol/l)	383.14 ± 91.75	368.06 ± 104.49	399.12 ± 74.23	0.158

*Values are reported as mean ± standard deviation.
BMI, Body Mass Index; p_value ≤0/05 was assigned as statistically significant.

GCBE among participants with dyslipidemia for 8 weeks had favorable results on Oxidized LDL, and TAC.

In agreement with the present trial, there are several studies that reported a similarly favorable effect of GCBE on metabolic variables. A meta-analysis on three trial studies revealed GCBE intake resulted in significant weight loss (−2.47 kg) [36]. In another study, Hanieh Roshan et al. reported 400 mg GCBE supplementation for 8 weeks resulted in significantly reduced systolic blood pressure (SBP), fasting blood glucose (FBS), and homoeostatic model of assessment of insulin resistance, waist circumference, and appetite score in comparison to placebo [37]. In addition, Revuelta-Iniesta et al. showed GCBE consumption reduced systolic blood pressure, BMI and abdominal fat [38], whilst Watanabe et al. demonstrated CGA in GCBE led to decreased blood pressure, body mass index, pulse rate, routine blood test, urinalysis, and hematochemistry [39]. Concordant with our study, Yukawa et al. reported that Oxidized LDL, as well as malondialdehyde (MDA) and thiobarbituric acid reactive substances (TBARS) were reduced after one week coffee consumption [40]. In addition, another study showed that a 4-week coffee intervention led to increased TAC and antioxidant enzyme activities, while there was no significant OX-LDL change [41]. However, recent empirical studies have not observed a significant change in OX-LDL following intervention of 800 ml/day of instant and filtered coffee [26,42]. Although it is evident that the composition of green coffee differs from black coffee (BC) due to the roasting process, different study designs, different dosages of coffee and polyphenol content, as well as duration of the study likely contribute to the varied results among studies related to OX-LDL.

The exact mechanism through which green coffee intake might influence OX-LDL is unknown. Ochiai R et al. reported that green coffee intake decreased plasma total homocysteine concentration [39]; thus green coffee intake may conceivably influence OX-LDL by reducing homocysteine, because homocysteine increases oxidation by promoting the formation of reactive oxygen species [43]. Recent evidence has shown that CGA has prominent antioxidant, anticarcinogenic activities and hypolipidemic effects, and is one of the most abundant polyphenol compounds in coffee [44–46]. The favorable effect of the GCBE administration on Oxidized LDL, and TAC may plausibly be mediated by polyphenols; in fact, our study found an association between serum TAC and green coffee antioxidant capacity that is confirmed in other studies [47–49]. Moreover, Fausta Natella et al. in a study on ten healthy, nonsmoking, moderate coffee drinkers reported phenolic compounds are likely to be responsible for the increase in plasma antioxidant capacity after coffee drinking [50]. In agreement with the present study, there are several human and animal-based studies that have reported polyphenol supplementation promoted antioxidant capacity [49,51,52]. In addition, the effect of GCBE supplementation on OX-LDL and TAC may be mediated through weight loss, because studies have shown that weight loss leading to significant reduction in OX-LDL and increase in TAC [53,54]. Interestingly, the control group of the present study also appeared to have an increase in TAC – although at a lower level than the intervention group, that this could only conceivably be attributed to the placebo effect; nevertheless, further work must be conducted to confirm the veracity of our results.

The strength of current trial lies in the double-blind, randomized, placebo-controlled design. However, there are several restrictions that need to be considered in interpreting the results of this study. Firstly, the trial was conducted on a small group of homogenous males at a single location and the limited age range that makes extrapolation to other populations difficult. Further studies would therefore benefit from incorporating larger sample sizes and different intervention populations. Moreover, we were unable to measure additional antioxidant variables in our study, and future investigations are required to examine the effect of GCBE consumption on antioxidant enzymes and other biomarkers of oxidative stress.

6. Conclusion

The current trial showed that the intake of 800 mg per day of GCBE may have favorable effects on TAC and OX-LDL in patients with dyslipidemia. However, further studies are necessitated to confirm the veracity of these results.

Table 2
The effect of green coffee extract supplementation on serum oxidized LDL cholesterol and total antioxidant capacity in patients with dyslipidemia.

	Intervention (n = 36)		Control (n = 34)		p-value[a]
	Mean ± SD	Mean Change	Mean ± SD	Mean Change	
Oxidized LDL(ng/ml)					
Baseline	63.82 ± 69.89	−16.08 ± 33.30	65.35 ± 80.18	15.10 ± 53.34	< 0.001
End of trial	47.74 ± 39.80		66.86 ± 42.38		
P-value[b]	0.006		0.870		
TAC (μmol/l)					
Baseline	368.06 ± 104.49	130.55 ± 134.75	399.12 ± 74.23	58.824 ± 83.40	0.029
End of trial	498.61 ± 110.87		457.94 ± 51.155		
p-value[b]	< 0.001		< 0.001		

[a] Obtained from ANCOVA (analysis of co-variance), adjusted for baseline values.
[b] Obtained from paired *t*-test.

Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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