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The interaction of FTO-rs9939609 polymorphism with artichoke leaf extract effects on cardiometabolic risk factors in hypertriglyceridemia: A randomized clinical trial

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ABSTRACT

Objective: Hypertriglyceridemia is associated with an increased risk of cardiovascular disease. The potential favorable effects of artichoke leaf extract (ALE) on anthropometric and metabolic indices may affect by fat mass and obesity associated (FTO)-rs9939609 polymorphism. This study was designed to evaluate the effects of ALE supplementation on cardiometabolic risk factors in hypertriglyceridemic patients regarding the interaction of rs9939609-FTO polymorphism with intervention outcomes.
Methods: In this double-blind placebo-controlled randomized clinical trial, 52 patients with hypertriglyceridemia randomly allocated to receive ALE (1800 mg/day as four tablets) or matching placebo (consisting of corn starch, lactose, and avicel) for 12 weeks. The measurement of anthropometric indices, fasting blood sugar (FBS), and lipid profile was performed before and after the intervention. The FTO-rs9939609 polymorphism was genotyped by polymerase chain reaction-restriction length polymorphism (PCR-RFLP). The interaction was tested using two-way ANOVA.
Results: Forty-eight patients completed the trial (intervention, n = 24, placebo = 24). ALE and placebo groups were similar in the baseline characteristics. ALE supplementation did not change anthropometric indices and metabolic parameters. However, there was a significant interaction between FTO-rs9939609 polymorphism and TC, LDL-C, and TG level response to ALE supplementation. Moreover, significant changes in TG level were observed in A allele carriers compared to subjects with TT genotype.
Conclusion: No significant effect of ALE supplementation was shown on anthropometric and biochemical indices in Iranian hypertriglyceridemic patients. However, rs9939609 variant of FTO gene seems to affect lipid profile response to ALE supplementation. Further clinical trials with larger sample size are suggested to clarify the possible interaction between rs9939609 variant or other variants of FTO gene and ALE supplementation in hypertriglyceridemia.

1. Introduction

Elevated serum levels of triglyceride have independently been associated with increased risk of cardiovascular disease [1]. Hypertriglyceridemia commonly coexist with multiple risk factors including prothrombotic and proinflammatory biomarkers, increased plasma glucose levels, hypertension, obesity and metabolic syndrome [2]. Furthermore, patients with very high serum levels of triglyceride (more than 10 mmol/L) are at risk for acute pancreatitis [3].

The fat mass and obesity associated (FTO) gene encodes an enzyme which is present in many tissues, especially in the hypothalamus, the center of energy homeostasis [4]. The rs9939609 polymorphism in FTO gene is a potential candidate genetic variant for obesity and metabolic syndrome [5–7]. Since hypertriglyceridemia is a common feature of obesity and metabolic syndrome [8], the FTO variant rs9939609 may be implicated in the

Abbreviations: ALE, artichoke leaf extract; CETP, cholesteryl ester transfer protein; DBP, diastolic blood pressure; FBS, fasting blood sugar; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDA, malondialdehyde; SBP, systolic blood pressure; TAC, total antioxidant capacity; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

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susceptibility to hypertriglyceridemia. Furthermore, A allele of rs9939609 variant gene of FTO, the risk allele of adiposity, is associated with higher triglyceride, insulin and glucose levels, and that these associations are dependent on body mass index (BMI) [7]. Differences in individuals' genetic background may modulate the effect of the intervention on outcome variables [6,9–14].

Artichoke (*Cynara scolymus* L., Asteraceae family) is used both as a healthy food and as a medicinal herb worldwide [15]. Traditionally, artichoke leaf extract (ALE) was used to treat dyspepsia and hepato-biliary diseases. Scientific researches indicated antioxidant [16–18], hepatoprotective [16,17], anti-atherosclerotic [19,20] and glucose and lipid lowering effects [21–24] for ALE. The safety of ALE supplementation has been demonstrated in animal and human studies. There were no reported mutagenic and genotoxic effects in mice at <2000 mg/kg [25]. Furthermore, only mild and transient adverse events relating to the gastro-intestinal system have been reported in some clinical trials following ALE consumption [22–26].

Recently, some clinical trials have shown the efficacy of ALE in improvement of triglyceride (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) concentration [14,21,22,24,27,28], whereas others failed to show any improvement [26]. Besides, rs9939609 variant in FTO have shown an association with higher triglyceride level [7]. To best our knowledge, there is limited evidence for effects of ALE supplementation on cardiometabolic parameters in hypertriglyceridemi patients. Thus, the present study was aimed to investigate the effects of artichoke leaf extract on cardiometabolic risk factors in hypertriglyceridemic patients and an interaction with rs9939609 variant in FTO gene.

2. Materials and methods

2.1. Study design and participants

The present randomized, double-blind, placebo-controlled clinical trial was a part of a case-control study on metabolic syndrome gene polymorphism with 185 sample size. The intervention part was carried out on hypertriglicerdemic patients. The sample size was calculated based on the changes in serum fasting blood sugar (FBS) level reported by Rondanelli et al. [24]. Considering a confidence level of 95% and power of 80% and anticipating a possible dropout rate of 10%, 26 patients with hypertriglicerdemia were selected for each intervention arm.

The case-control study was aimed to explore the possible association of metabolic syndrome and gene polymorphism of FTO, TCF7L2, and CETP. This study was comprised of 80 patients with metabolic syndrome and 100 healthy participants (unpublished results). All the participants were screened at the beginning of the study, and among them we included 52 eligible patients with hypertriglicerdemia to examine the effects of ALE supplementation on cardiometabolic indices based on calculated sample size.

In this study, fifty-two patients aged 20–50 years old with triglyceride level 150–400 mg/d were recruited in Khoy, Iran from November 2014 to May 2015. Patients with history of any clinically diagnosed disease; intake of anti-hypertensive, corticosteroids or fat-lowering medications; and antioxidant supplements were excluded. Moreover, being hypersensitive to artichoke family plants, being current smoker, as well as pregnancy, lactation, and menopause were among exclusion criteria. All eligible subjects were asked to sign the written informed consent. The experimental protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences and it was registered at the Iranian Registry of Clinical Trials (http://www.irct.ir/) (code: IRCT201409033320N9).

The subjects were randomized (1:1) into ALE or placebo group using permuted block randomization procedure (blocks of four) after stratification by sex and age. Random allocation software (RAS) was used to create the allocation sequence. The codes were printed on the supplement boxes according to a random number sequence, which was generated by software. Then, the coded bottles were handed over to the eligible patients. The allocation was done by a statistician who was not involved in the clinical procedures of the study. Moreover, all the researchers involved in this study, remained blind during the intervention until data analysis. ALE and placebo tablets were provided in similar opaque plastic bottles. The bottles were given to the subjects at two time points: at baseline and in the middle of the interventions period.

The ALE group received 1800 mg/day of ALE as four tablets and the placebo group received a similar amount of cornstarch, lactose and avicel for three months. They were requested to take supplements before three main meals (one before breakfast, two before lunch, and one before dinner). The subjects were asked to return the remaining tablets to determine the compliance to the supplementation regimen.

2.2. Supplements preparation

ALE and placebo tablets were prepared by the Dineh Iran Co (Qazvin-Iran) in the same color and size. Artichoke (Cynara cardunculus var. scolymus L.) leaves with a botanical voucher specimen (93H026-191) were used for extraction, which were collected from the Iran's Medicinal Plants Cultivation Company. The alcoholic extraction (EtOH 70%) was used to prepare ALE. The extract was characterized by at least 4–5% chlorogenic acid using the spectrophotometer (505 ± 2 nm), based on the protocol of Iranian Herbal pharmacopoeia [29].

2.3. Clinical measurements

Blood samples were obtained after 12-hr overnight fasting, at the beginning and end of the intervention. Samples were centrifuged at 3000 rpm for 10 min to separate serum. Serum levels of FBS, total cholesterol (TC), high-density lipoprotein (HDL-C), and triglyceride (TG) were determined by enzymatic colorimetric methods with Pars-Azemoon kits (Tehran, Iran) on an automatic biochemical Hitachi 717 analyzer (Hitachi, Boehringer Mannheim, Japan). Serum low-density lipoprotein (LDL-C) level was calculated using Friedewald equation, as follows: LDL-C = TC-(HDL-C + TAG/5) [30].

Furthermore, serum cholesteryl ester transfer protein (CETP) concentration was assayed using human ELISA kit (Eastbiopharm, Hangzhou, china). Serum total antioxidant capacity (TAC) levels were measured by Abbott Alcyon 300 auto analyzer (Abbott Park, IL, USA), using commercial kits (Randox, Crumlin, UK). Serum malondialdehyde (MDA) levels were determined based on their ability to react with thiobarbituric acid (TBA), which produced a pink colored complex. Then, absorption measurement was performed using spectrophotometer at 532 nm (Kontron, model SFM 25 A; Milan, Italy) and compared to the standard curves.

At baseline and end of the study, anthropometric indices including height, weight, waist circumference (WC) and hip circumference (HC), and blood pressure (BP) were measured using calibrated equipment as have been explained elsewhere [31]. Furthermore, body mass index (BMI) (weight (in kilogram)/height (in meters squared)) and waist-to-hip ratio (WHR) was calculated.

2.4. Genetic assessments

Blood samples were stored in tubes containing ethylenediaminetetraacetic acid (EDTA) at −80 °C. The rapid DNA genomic extraction (RDGE) method was used to extract the genomic DNA. The polymerase chain reaction (PCR), followed by restriction

fragment length polymorphism (RFLP) method with mismatch primer modification was applied to determine the single nucleotide polymorphisms (SNPs) of FTO-rs9939609, as previously have been explained in detail [32]. The following PCR primers were used: 5′-CTAGGTTCCTTGCGACTGCTGTGAACT-3′ (forward) and 5′-TTCAAGTCACACTCAGCCTCTCTACCA-3′ (reverse). The PCR product was incubated at 37 °C for 16 h with DdeI restriction enzyme (Thermo Scientific, Vilnius, Lithuania). The digestion products were resolved by electrophoresis on a 12% sodium dodecyl sulfate (SDS)-polyacrylamide gel and then treated using ethidium bromide. Upon running the resulting fragments, the A allele produced 189- and 26-bp bands and the T allele produced a 215-bp band.

2.5. Statistical analyses

All data analyses were performed using SPSS version 16 (SPSS, Chicago, USA). The normality of data distribution was tested using the Kolmogorov-Smirnov test. Since CETP concentration was not symmetrically distributed, logarithm transformation was done, and data was presented as logarithmic mean (minimum, maximum). The results are expressed as mean ± standard deviation (SD) and number (percent) for quantitative and qualitative data, respectively. At baseline, the possible differences between groups were evaluated by independent sample *t*-test. Moreover, to assess differences in properties, chi-square test was employed. For detection the effect of intervention, FTO-rs9939609 polymorphism, and gene-intervention interaction on changes of cardiometabolic factors, two-way ANCOVA test was used with adjustment for baseline values as covariates. Whilst, this analysis was not performed on the CETP, MDA, and TAC due to no possible association of them with FTO-rs9939609 polymorphism based on previous studies [7,10,12]. $P < 0.05$ was set as statistical significance.

3. Results

Of the 185 subjects who were screened for FTO-rs9939609 polymorphism, 25.9% (n = 48) were homozygous for T allele, 65.4% (n = 121) were heterozygote, and 8.6% (n = 16) were homozygous for C allele (data not shown). During the 12-week follow-up, four patients were withdrawn from the study (2 patients from each intervention and placebo group) as shown in Fig. 1. None of the dropouts were related to the adverse effects of ALE or placebo. Moreover, there were no reports of adverse effects in neither of the groups throughout the trial. The baseline anthropometric and biochemical characteristics of the patients, as well as, the allele frequency of FTO-rs9939609 polymorphism are shown in Table 1. The mean age of the patients was 38.44 ± 6.73 yrs. and 35.4% of them were male. At the beginning of the study, there were no differences between groups in any of the measured parameters.

The results of two-way analysis of covariance (ANCOVA) with adjustment of baseline values on the effects of intervention, FTO-rs9939609 polymorphism and the intervention-genotype interaction in subgroups of FTO-rs9939609 polymorphism in ALE and placebo group are shown in Table 2. There were no significant changes in anthropometric indices, biochemical variables and blood pressure in response to ALE supplementation compared to placebo. But dependent on the FTO-rs9939609 polymorphism, TG level was changed significantly after the intervention. Furthermore, the interactive effect of ALE supplementation and FTO-rs9939609 polymorphism were observed on serum levels of TC, LDL-C and TG.

4. Discussion

The present study was found that ALE supplementation did not change the anthropometric and biochemical variables in patients with hypertriglyceridemia over 12 weeks. However, the significant interaction between ALE supplementation and FTO-rs9939609 polymorphism was found on TC, LDL-C and TG level. Moreover, TG level significantly affected by FTO-rs9939609 polymorphism regardless of intervention.

The FTO gene, located on chromosome 16q12.2, encodes a nuclear protein of non-haem Fe(II) and 2-oxoglutarate-dependent dioxygenases superfamily. This gene is commonly expressed in human tissues, but its exact physiological function is not fully understood [4]. Recent evidence indicated that individuals carrying mutant allele of rs9939609 have been found to be at increased risk for obesity, metabolic syndrome, and type 2 diabetes mellitus [6,7]. Human studies have found that the risk allele of rs9939609 SNP is associated with greater BMI, increased food

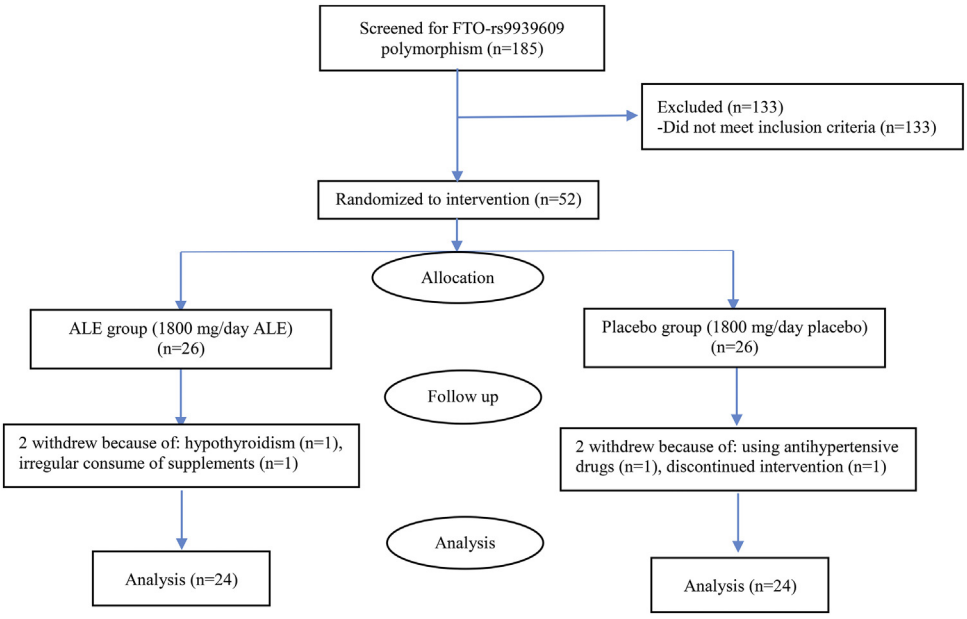

Fig. 1. Flow diagram of the study.

Table 1
Baseline characteristics of study subjects.

Variables	ALE group (n = 24)	Placebo group (n = 24)	p †
Age (year)	38.0 ± 6.9	38.8 ± 6.5	0.688
Weight (kg)	91.9 ± 11.8	87.1 ± 16.6	0.263
BMI (kg/m^2)	34.4 ± 3.7	32.8 ± 4.0	0.726
WC(cm)	108.6 ± 6.4	106.2 ± 10.7	0.346
HC (cm)	114.8 ± 7.0	113.5 ± 8.4	0.588
WHR	0.94 ± 0.06	0.93 ± 0.07	0.537
FBS (mg/dl)	97.39 ± 8.70	96.71 ± 8.59	0.788
TC (mg/dl)	203.4 ± 39.2	190.4 ± 38.6	0.297
HDL-C (mg/dl)	41.5 ± 9.8	40.3 ± 9.1	0.678
LDL-C (mg/dl)	110.8 ± 31.0	104.3 ± 25.7	0.469
TG (mg/dl)	243.6 ± 79.1	212.7 ± 72.4	0.165
SBP (mmHg)	129.6 ± 19.7	125.7 ± 13.3	0.418
DBP (mmHg)	84.0 ± 7.7	81.1 ± 6.7	0.174
CETP (μg/ml)€	1.20 (.97, 1.57)	1.17 (1.01, 1.55)	0.532
TAC (mmol/L)	1.75 ± 0.28	1.83 ± 0.37	0.370
MDA (nmol/ml)	2.96 ± 0.84	2.73 ± 0.52	0.194
Sex, n (%)			0.763
Male	8 (33.3)	9 (37.5)	
Female	16 (66.7)	15 (62.5)	
FTO-rs9939609, n (%)			0.204
A allele	19 (79.2)	15 (62.5)	
TT	5 (20.8)	9 (37.5)	

BMI: body mass index; WC: waist circumference; HC: hip circumference; WHR: waist to hip ratio; FBS: fasting blood sugar; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride; SBP: systolic blood pressure; DBP: diastolic blood pressure; CETP: cholesteryl ester transfer protein; TAC: total antioxidant capacity; MDA: malondialdehyde.
Values are mean ± SD, unless otherwise mentioned.
€ Analysis are based on geometric logarithmic mean (minimum, maximum).
† Independent sample *t*-test and or Pearson Chi-Square test for numeric and categorical variables, respectively.

Table 2
The effect of ALE supplementation, FTO-rs9939609 polymorphism, and ALE-rs9939609 variant of FTO gene interaction on anthropometric and biochemical parameters.

Variables	At the baseline				At the end				p†		
	ALE group (n = 24)		Placebo group (n = 24)		ALE group (n = 24)		Placebo group (n = 24)				
	TT (n = 5)	A allele (n = 19)	TT (n = 9)	A allele (n = 15)	TT (n = 5)	A allele (n = 19)	TT (n = 9)	A allele (n = 15)	Intervention††	Genotype**	Interaction‡
Weight (kg)	89.7 ± 11.2	92.5 ± 12.2	89.5 ± 16.2	85.6 ± 17.2	89.6 ± 11.4	92.4 ± 11.5	88.8 ± 16.2	84.9 ± 17.0	0.184	0.889	0.785
BMI (kg/m^2)	33.2 ± 3.1	34.8 ± 3.8	34.0 ± 4.1	32.0 ± 3.9	33.2 ± 2.9	34.9 ± 3.7	33.8 ± 4.4	31.7 ± 3.9	0.177	0.808	0.502
WC(cm)	107.6 ± 7.0	108.9 ± 6.4	107.6 ± 14.8	105.4 ± 8.2	106.6 ± 7.4	108.3 ± 5.9	107.1 ± 14.6	103.4 ± 8.4	0.450	0.459	0.184
HC (cm)	116.0 ± 8.1	114.5 ± 6.9	116.3 ± 8.4	111.9 ± 8.3	115.6 ± 9.0	114.7 ± 7.1	116.3 ± 8.4	111.0 ± 6.8	0.492	0.629	0.218
WHR	0.92 ± 0.06	0.95 ± 0.06	0.91 ± 0.09	0.94 ± 0.06	0.92 ± 0.08	0.94 ± 0.06	0.91 ± 0.09	0.93 ± 0.06	0.642	0.745	0.809
FBS (mg/dl)	97.75 ± 9.74	97.32 ± 8.76	95.11 ± 7.88	97.67 ± 9.11	96.50 ± 6.55	95.32 ± 8.09	93.67 ± 3.31	94.47 ± 9.09	0.561	0.677	0.962
TC (mg/dl)	205.0 ± 37.4	203.0 ± 40.8	184.8 ± 40.2	193.2 ± 39.3	210.8 ± 43.4	182.8 ± 31.5	160.5 ± 36.0	182.6 ± 40.0	0.103	0.594	**0.024**
HDL-C (mg/dl)	43.7 ± 5.7	40.9 ± 10.7	39.3 ± 11.9	41.0 ± 6.8	48.1 ± 9.7	41.5 ± 9.9	40.5 ± 8.5	40.0 ± 9.0	0.187	0.191	0.504
LDL-C (mg/dl)	117.7 ± 32.2	108.6 ± 31.4	111.5 ± 26.0	98.4 ± 25.0	118.3 ± 33.2	96.1 ± 24.1	99.8 ± 22.9	95.3 ± 24.8	0.466	0.287	**0.036**
TG (mg/dl)	212.0 ± 56.2	252.0 ± 83.3	212.2 ± 44.8	213.0 ± 86.4	175.0 ± 51.8	193.7 ± 68.8	136.44 ± 54.0	227.0 ± 96.3	0.686	**0.042**	**0.027**
SBP (mmHg)	125.4 ± 10.2	130.8 ± 21.6	124.1 ± 8.9	126.6 ± 15.6	119.2 ± 17.9	126.2 ± 17.0	120.7 ± 7.4	121.0 ± 14.3	0.914	0.696	0.504
DBP (mmHg)	81.8 ± 8.1	84.6 ± 7.7	81.0 ± 5.7	81.2 ± 7.5	78.2 ± 9.0	79.9 ± 7.7	79.3 ± 6.5	78.4 ± 10.5	0.461	0.686	0.898

BMI: body mass index; WC: waist circumference; HC: hip circumference; WHR: waist to hip ratio; FBS: fasting blood sugar; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride.
Values are mean ± SD. P-values of statistical significance ($p < 0.05$) are presented in bold.
† Two-way ANCOVA test, adjusted for baseline values.
†† The effect of ALE on outcome variable.
** The effect of FTO-rs9939609 on outcome variable.
‡ The gene-intervention interaction on outcome variable.

intake and lowered satiety/greater hunger, whereas is not associated with energy expenditure [33].

The rs9939609 SNP in FTO is a common genetic variant with variation in frequency in different ethnic groups. In our study, the frequency of the mutant allele was 70.8%, which was higher than the worldwide (64%) and lower than Asian population (84%) reported prevalence [34].

In the present study, the response of serum level of TC, LDL-C and TG to ALE supplementation revealed a significant interaction with FTO-rs9939609 polymorphism. Furthermore, the significant interaction was found between genotype and TG level, regardless of supplementation. Several interventional studies have found an interaction between diet/lifestyle modification and the rs9939609 polymorphism of FTO gene, although the results are inconsistent. Razquin et al. (2010) found that in A allele carriers of FTO-rs9939609 polymorphism, body weight gain was lower than TT carriers after a 3-year Mediterranean-style diet, irrespective of the type of nutritional intervention [10]. In a study by de Luis et al (2012), low-carbohydrate or low-fat hypocaloric diets in obese subjects did not show any association with FTO-rs9939609 SNP after 12 weeks. But, in low-fat diet group, c-reactive protein (CRP), TC and LDL-C level significantly reduced in subjects carrying A allele compared to subjects carrying non-mutant allele [11]. Muller et al (2008) also reported no significant association between variant rs9939609 and weight loss or lipid profile modifications in a lifestyle intervention in obese children and adolescents [12]. In a study on subjects with impaired glucose tolerance (IGT) by Lappalainen et al (2009), rs9939609-FTO did not associate with weight loss in a 4-year lifestyle modification [13]. A recent meta-analysis indicated that weight loss secondary to diet/lifestyle interventions in carriers of risk allele (A) significantly was higher than noncarriers [6]. These diverse results may be explained by differences in type of intervention, ethnicity and background health status of the participants. Moreover, another possible reason for varying results across studies is different statistical analysis methods which used to test the interaction between intervention and genotype.

The present study showed that ALE supplementation could not affect the anthropometric indices, blood pressure and lipid profile in hypertriglyceridemic patients. Our findings are in line with Rnodanelli et al. (2011) 's study. They reported that a mixture of 600 mg of Cynara scolymus (Cs) flowering buds extract and 300 mg of Phaseolus vulgaris (Pv) extract did not change TG, TC and LDL-C level, as well as, weight and BMI in overweight subjects after 8 weeks [26]. Also, Petrowicz et al. (1997) found that 1920 mg ALE did not reduce TC level in healthy adults after 12 weeks. Only in subgroup analysis in subjects with baseline TC > 230 mg/dl, TC level significantly decreased at the end of the intervention [35]. However, based on Englisch et al. (2000) study, 1800 mg aqueous extract of artichoke significantly reduced TC and LDL-C level in patients with hypercholesterolemia (TC > 280 mg/dl) after 6 weeks. But, ALE supplementation failed to reduce TG level [21]. Also, Bundy et al. (2008) showed that consumption of 1280 mg ALE resulted in significantly decreased TC level in healthy adults with mild hypercholesterolemia (TC at 232–309 mg/dl) after 12 weeks, without significant reduction of serum level of HDL-C, LDL-C and TG [22]. Rnodanelli et al. (2014) also found significant reduction of TC, LDL-C and BMI in overweight patients with impaired fasting glycaemia (IFG) in response to 600 mg Cs extract supplementation after 8 weeks [24]. It seems that differences in given dosage of ALE, baseline level of lipid profile, background disease and amount of bioactive ingredients of ALE may have contributed to the inconsistencies in results of the studies.

The hypolipidemic effects of ALE have been indicated in animal models and some clinical trials [22,24,36–38]. Beneficial effects of ALE on improving TG level may be related to several bioactive components found in ALE, including sesquiterpens (grosheimin, aguerin B and cynaropicrin) and sesquiterpene glycosides (cynarascolosides A, B, and C). Also, hypotriglyceridemic effect of ALE may be mediated through inhibition of gastric emptying [36]. In addition, the possible hypocholesterolemic effect of ALE could be associated to increase the bile production and partial inhibition of biosynthesis of cholesterol [38,39].

In the present study, only five participants had the TT genotype in ALE group which likely decreased the power of study to explore the interaction between cardiometabolic parameters and FTO-rs9939609 polymorphism. The sample size calculation was based on our primary outcome (effects of ALE on cardiometabolic indices), and the interaction analysis between genotype and intervention response was the second outcome. Results would be more reliable if a larger sample size was studied. Based on our finding regarding LDL-C differences in A allele subgroup, considering a confidence level of 95% and power of 80%, at least 69 patients were needed per group. Estimating a possible dropout rate of 10%, 304 patients with hypertriglicerdemia were required to confirm our results. Overall, the interaction analysis in this study provided some interesting preliminary and exploratory results for further analysis, however this is highly speculative, and needs to be confirmed in future larger trials.

The limitations of the current study are as follows: the active ingredients of ALE were measured by spectrophotometry, which has less accuracy than high-performance liquid chromatography (HPLC). Moreover, sample size was relatively small in genotype subgroups. The present study had some strengths. The design of the study was randomized double blind and intervention-genotype interaction was evaluated. Furthermore, two-way ANCOA test with adjustment for baseline variables was used for statistical analysis.

5. Conclusion

Our finding showed that ALE supplementation did not affect anthropometric and biochemical indices in Iranian hypertriglyceridemic patients. Moreover, this study suggested the interaction between the response of lipid profile to ALE supplementation and FTO-rs9939609 polymorphism.

Accordingly, polymorphism genotyping helps the clinicians in choosing the appropriate treatment for patients with hypertriglyceridemia. Moreover, individuals carrying A allele of FTO-rs9939609 polymorphism may benefit more from artichoke consumption than TT genotype. Further clinical trials with a larger sample size are needed to describe whether rs939609 variant of FTO gene be able to affect responses to ALE supplementation in hypertriglyceridemic patients.

Conflict of interest

The authors declare that they have no conflicts of interest.

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